Middle East Cancer Consortium (MECC) International Pediatric Oncology Meeting Abstracts

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Treatment of Wilms Tumor: A Report From the Turkish Pediatric Oncology Group (TPOG)

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Aim: The aim of this study was to standardize the diagnosis and treatment of Wilms tumor (WT) in Turkey.

Methods and Patients: From January 1998 to December 2006, WT patients were registered from 18 pediatric oncology centers. Eligibility criteria were age < 16 years, a clinical, radiologic, and histopathologic diagnosis of unilateral WT, treatment started in the first postoperative 3 weeks. Patients > 6 months of age with either inoperable tumors or inferior vena cava involvement received 4 weeks of preoperative chemotherapy with "vincristine (VCR) + actinomycin-D (Act-D)." Treatment plans were stage I favorable (FH) and unfavorable histology (UH) patients, "VCR + Act-D" (6 mo); stage IIA FH, "VCR + Act-D" (6 mo); stage IIB FH, "VCR + Act-D" (12 mo) + radiotherapy (RT); stages III and IV FH, "VCR + Act-D + adriamycin (ADR)" (12 mo) + RT; stages II, III, and IV UH tumors, "VCR + Act-D + ADR + etoposide" (18 mo) + RT.

Results: Of 251 registered cases (15 bilateral, 6%) 162 were eligible (median age 3.0 y; range, 0.4 to 16 y, M/F: 1.04). Forty-nine cases (30.2%) were equal or younger than 2 years. Number of cases in different stages were stage I, 37 (22.8%); IIA, 61 (37.7%); IIB, 8 (4.9%); III, 37, (22.8%); IV, 19 (11.8%) (18 lung, 2 liver, 1 skeletal metastases). One hundred forty-six cases had FH and 16 (9.9%) had UH tumors. Twenty-two cases (13.6%) received preoperative chemotherapy. Cases older than 2 years had more stage III or IV disease compared with younger ones ($P = 0.014$). There was no significant difference between the 2 age groups according to the presence of unfavorable histology.

Eleven cases (stages: I, 2; IIA, 6; IV, 3) experienced a recurrence of disease at a median of 13.1 months (6 to 52) and were treated accordingly. Sites of recurrences were the primary tumor sites and/or abdomen, 8 cases; lungs, 2; contralateral kidneys, 2. Nine of these cases were alive with no evidence of disease and 2 died (median follow-up, 38 mo; range, 12 to 97). Two cases who experienced progressive disease died despite salvage therapies. Five other cases died due to early postoperative complications (n = 1), neutropenic fever (n = 1), cardiomyopathy (n = 1), secondary cancers (1 AML + medulloblastoma; 1 osteosarcoma of the mandible). Eleven cases were lost to follow-up (median time, 5.6 mo; range, 0.5 to 22.3 mo). Survival data is given in the Table 1.

Conclusions: This is the first national experience with a multicentric study in pediatric oncology in Turkey. Despite problems in patient management and follow-up, treatment results are encouraging. Revisions and modifications are planned to further improve the results and minimize short and long-term side effects.

TABLE 1. Five-year Overall and Event-free Survival Rates in Wilms Tumor Cases (TPOG)

	n	Overall Survival (%)	Event-free Survival (%)
All patients		94.3	86.3
Stages			
I	37	100	93.1
IIA	60	96.5	88
IIB	8	100	100
III	37	97.1	97.1
IV	20	48.7	33.8
P		< 0.0001	< 0.0001
Histopathology			
Favorable	146	95.3	87.9
Unfavorable	16	70.5	70.5
P		0.016	0.3
Ages			
≤ 2 y	49	90.8	83.2
> 2 y	113	93.6	87.8
P		0.3	0.33

Participating Centers:
Hacettepe University Faculty of Medicine, Ankara; İstanbul University Cerrahpaşa Faculty of Medicine, İstanbul; Akdeniz University Faculty of Medicine, Antalya; Bakırköy Education and Research Hospital, İstanbul; Göztepe Education and Research Hospital, İstanbul; Kartal Education and Research Hospital, İstanbul; Dokuz Eylül University Faculty of Medicine, İzmir; İstanbul University Institute of Oncology, İstanbul; Gazi University Faculty of Medicine, Ankara; Karadeniz Technical University Faculty of Medicine, Trabzon; Ondokuz Mayıs University Faculty of Medicine, Samsun; Kocaeli University Faculty of Medicine, Kocaeli; Mersin University Faculty of Medicine, Mersin; Çukurova University Faculty of Medicine, Adana; Ankara University Faculty of Medicine, Ankara; Dr Sami Ulus Children's Hospital, Ankara; Ege University Faculty of Medicine, İzmir; Trakya University Faculty of Medicine, Edirne, Turkey.

Pediatric Stem Cell Transplantation in Turkey

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Hematopoietic stem cell transplantation offers a long-term disease-free survival for many patients with malignant or nonmalignant, acquired or congenital disorders. Hematopoietic stem cell transplantations have rapidly increased over the last decade and the increasing demand can present a challenge for health care systems. Since 1891, when B-Sequard d'Arsonaval has applied the first BMT orally, important advances have been gained in this area. More than 40,000 hematopoietic cell transplants are performed worldwide each year. During the last decade, major changes have occurred in clinical practice based on new scientific and technical developments. Major changes have occurred concerning donor type, stem cell source, indications, and technology. New or changed indications has been proposed and applied. The increasing use of alternative stem cell sources such as peripheral blood stem cells and cord blood also affected the overall outcomes and complications. With improvements in transplant technology, more transplant recipients now survive free of the disease for which they were transplanted.

Since 1988, 10 pediatric centers have applied 811 (621 allogeneic, 190 autologous) SCTs in Turkey. The distribution of patients according to the centers and type of SCT is summarized in the Table 1. The main indications were leukemias (219 cases), T. Major (151 cases), SCID, solid tumors, etc. Among 219 leukemia cases, 129 were AML, 45 ALL, 22 CML, 17 MDS, and 6 JMMoL. Among solid tumors, neuroblastoma was the main indication. Before 2003, 23 cases had SCT and 52% is alive and well. But after 2003, 19 cases had SCT and 70% is alive and well with a shorter follow-up. About 43% of 28 patients with Hodgkin disease, 50% of 12 NHL patients are alive and well. One hundred fifty-one SCTs in 136 patients were applied for hemoglobinopathies. Overall survival for this group was 85.5% and survival without thalassemia 74.1% for 17 years.

TABLE 1. The Distribution of Patients According to the Centers and Type of SCT in Turkey

Pediatric SCT Centers	Allogeneic	Autologous	Total
OCLF/İUİMF	132	67	199
Hacettepe	176	2	178
Akdeniz	107	20	177
Ankara	75	12	87
Ege	33	22	55
Izmir-SSK	44	25	69
Çukurova	30	19	49
GATA	12	10	22
İstanbul UİMF	11	6	17
Gazi	1	7	8
All centers	621	190	811

Current use and trends in SCT will change in coming decades and prospective evaluations will be needed to assess the role of hematopoietic SCT in a wide spectrum of diseases. In Turkey, increasing number of

centers will provide SCT opportunity for more children and this will surely contribute to the overall outcomes of many diseases that can be cured by SCT.

New Horizons in Childhood Radiotherapy

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Care on pediatric cancers and awareness have been gradually improving with a significant increase in 5-year OS rates (56% in 1970s→78% in 1990s). The factors involved in this improvement are better understanding the biology of tumors and refinement and advances in oncologic surgery, radiation oncology, and diagnostic radiology, besides new chemotherapeutic agents. We have intentionally stepped back in radiotherapy in terms of indications, timing, and treated volumes due to demonstrated obvious late effects of high radiation doses leading to growth retardation, function impairment, carcinogenesis, and neurocognitive deficits.

One of the best examples of limited indications is what happened for Wilms tumor. Today radiotherapy is not offered to a subgroup of postnephrectomy favorable histology patients for stages I and II tumors in American NWTS V, and it is only recommended for stages III, IV favorable histology and II to IV with focal anaplasia, besides stage I to IV clear cell and II to IV diffuse anaplastic patients. European SIOP-treatment strategy also started to base on risk and stage groups and has prescribed radiotherapy for only intermediate risk with stage III and high risk with stage II and III patients.

Radiotherapy treatment volumes have been reduced over the years as it is the case in Rhabdomyosarcoma (RMS) patients though radiotherapy is still a key factor in treatment of RMS and being offered to all patients except groups I and II embriyonal RMS patients. Fields have been reduced from compartmental irradiation to gross tumor volume plus margin without elective nodal treatment. Doses, as well, are being investigated for further reduction.

In an attempt to decrease the risk of late sequela in medulloblastoma patients, craniospinal radiotherapy dose has been considerably reduced in average risk group from 36 to 23.4 Gy by the help of chemotherapy and further reduction is under investigation.

Treatment strategies have been revised based on risk adapted chemotherapy and response adapted radiotherapy especially in Hodgkin disease, through German Hodgkin's studies and Stanford/Dana Farber/St Jude protocols derived from 3 risk groups and involved field radiotherapy concept. Still radiotherapy has strengthened its position in disease-free survival in phase 3 Children Cancer Group and German trials testing radiotherapy omission (IFRT vs. observation in complete responders, Nachman et al, 2002 and Dorffel et al, 2003), no radiotherapy after complete response in PET after chemotherapy is also being tested in the German trial.

Despite all these limitations, radiotherapy continues to be mandatory as a part of the primary curative approach in many pediatric malignancies. Current pediatric radiotherapy is more precise with recent high-tech developments such as 3-dimensional conformal RT (3DCRT), intensity modulated RT (IMRT), stereotactic radiosurgery (SRS) and proton beam therapy. 3DCRT provided a better normal anatomy and tumor volume definition, optimal radiation ports and shielding, homogeneous and high target doses and optimal sparing in normal tissues. IMRT brought additional advantages as nonuniform beam intensity (0% to 100% intensity in beamlets), multiple simultaneous doses, more conformality and more normal tissue sparing; however, IMRT is not standard yet due to limitations of high total body and integral dose which may predispose increasing risk of second malignancies. SRS offered a very precise focal treatment with rapid dose fall-off and is found to be suitable for lesions with minimal peripheral invasion, easily demonstrable for treatment planning and spherical and small (generally < 3 to 4 cm). The most promising radiation modality for this age group is the proton beam therapy with its low entrance and almost no exit dose, maximum dose delivery at target (Bragg peak advantage) and improved normal tissue sparing. Nevertheless it should be kept in mind that it is rather expensive and not widely available.

In summary, in pediatric age group, radiation should be avoided or postponed whenever possible, and delivered precisely with the smallest and the lowest effective fields and doses when indicated. It should be remembered that radiation oncologists are "human beings" who love children and care about their future and it is our hope to cure our children with minimal oncologic treatment.

Molecular and Clinical Analysis of Turkish Patients With HLH

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Familial hemophagocytic lymphohistiocytosis (FHL) is a rare autosomal recessive, if untreated, fatal disorder of early childhood characterized by persistent fever, hepatosplenomegali, bicytopenia or pancytopenia, high ferritin, high triglyceride or low fibrinogen levels, decreased NK cell activity, increased alfa chain of soluble IL2 receptor level, hemophagocytosis by macrophages in bone marrow, lymph nodes, liver, and spleen. FHL is a genetically heterogeneous disease, 4 subtypes have been described to date. FHL type I has been mapped to long arm of chromosome 9, but the gene has not been identified yet. Type 2 is associated with inherited mutations in Perforin 1 gene, type 3 results from the mutations in human Munc 13-4 gene and type 4 has been associated with Syntaxin 11 gene. There are also FHL cases not being associated with any of these 4 described loci. Herein, we present the preliminary results of our ongoing study on evaluation of the genetic defects and associated clinical phenotypes in Turkish patients with FHL. So far, a total of 41 unrelated families were included in the study, 33 of these families were consanguineous, 18 had more than one affected children. The ages of diagnosis ranged from 7 days to 16 years with the median age of 1 year 2 months. Twenty-four patients were males, 17 were females and each patient fulfilled the diagnostic criteria of the Histiocyte Society. Linkage analysis was used in subtyping the patients to 1 of 4 described chromosomal loci by using 5-10 polymorphic microsatellite markers specific to flanking sequences of each gene. At the end of haplotype analysis; either homozygosity or consanguineous common alleles in parents of patients whose DNA were not available for the study was observed in 10 families for the perforin-1 gene, 18 families for hMunc13-4 gene, 6 families for Syntaxin 11 gene, 1 family for the unknown gene on chromosome 9. To date, molecular pathologies of Perforin 1 gene was reported to be the most common cause of the disease. In contrast, the preliminary results of this study indicated that not perforin (25%), but Munc13-4 gene (44%) defects may account for the pathologies of the highest proportion of all Turkish FHL cases, followed by Syntaxin 11 (15%) and unknown gene (3%) defects. Altogether, molecular pathologies of these 4 described loci may account for at most 87% of all Turkish FHL cases studied. We then searched for the possible pathologic mutations in 10 families linked to the Perforin 1 gene by direct sequencing of coding exons of the gene. To date, 5 different homozygous mutations were identified in 7 unrelated families. Three families had nonsense Trp374Stop mutation. The rest 4 families had different missense mutations: Gly149Ser, Val50Met, Ala91Val, and Ala523Asp. All the patients with perforin mutations were coming from consanguineous families; 4 were males, 3 were females, all had systemic presentation symptoms but the presentation ages were different. One patient with Trp374Stop mutation had symptoms at birth, diagnosed at the age of 7 days, and died 2 days after diagnosis without having chance to get treatment. Other 2 patients with this mutation 4 and 6-month old at time of diagnosis and died 7 days and 1 month after diagnosis, respectively. One patient with missense had rather early onset of the disease, at the age of 11 days, got treatment, relapsed 2 times, and died 10 months after diagnosis. In contrast, 2 patients had quite late-onset of disease; they first had CNS findings at the ages of 15 and 12 years; therefore, they were diagnosed 1 year later when they also developed systemic symptoms. After treatment, they survived. Last patient with missense mutation had systemic presenting symptoms at 34 months, died 3 months later. Currently, we are screening 18 patients linked to the Munc13-4 gene for mutations by using SSCP/HD and sequencing analysis. So far, we identified a frameshift mutation (627delT) in a female patient who also had heterozygous Ala91Val

mutation in the perforin gene. She was coming from a consanguineous family; diagnosed at the age of 20 months when the disease was presented with the systemic symptoms. She underwent BMT 3 months after diagnosis, she is 39 months old and doing very well right now. This study was supported by TUBITAK (Project No: 105S386; SBAG-3193).

Incidence Rate and Time-trends of Childhood Lymphomas in Israel and Other Middle Eastern Countries

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Introduction: Cancer in childhood (intended as cancer occurring under 15 y of age) is a relatively a rare event and includes 1.5% of all malignant diseases diagnosed in a population. Among childhood cancers, the second or third (usually depending on the country's development status) most frequent site is the Lymphoma group. Observing differences among countries and populations as well as difference along time in the disease occurrence can hint or direct toward possible etiologic factors. Using a population-based tumor registry is the most precise way to examine those changes.

Material and Methods:

Cancer Registration in Israel: The Israel National Cancer Registry (INCR) is a population-based, national tumor registry that was established in 1960. Since 1982 notification to the registry is mandatory by law, and all medical facilities reports to the registry. Registration is being conducted according to international standards using the ICD-O coding system. Demographical data on cancer patient is being retrieved from the central population registry using a unique personal identification number given to all Israeli citizens upon birth or immigration. The Israeli population is composed of 2 distinct ethnic groups: Jews who comprises 80% of the population and Arabs. This distinction is important when examining adult cancer epidemiology incidence and trends, as rate in the Arab population are generally significantly lower than those observed in the Jewish population.

Sources of Data: Data on Lymphomas were retrieved according to morphology codes from the INCR's database for the period 1970 to 2005. Standardized rates (using the world standard population) were calculated and presented. Additional comparative data were taken from the MECC comparative incidence monograph that refers to the period 1996 to 2001.

Results: Incidence rate for all lymphomas combined are relatively high in Israel where Arab presented a higher incidence rate (24 per Million) than Jews (20/M). These rates are higher than those reported in the United States (13/M) and several European countries (11/M in the UK, 14.5/M in Germany, and 13.8/M in Sweden). In the Middle Eastern area rates are generally higher than in United States and Europe where Turkey had a rate similar to Israeli Jews (19.7/M), Jordanians (19/M), and Cypriot children had a rate of 15.7/M. Exceptional high rates were observed in Egypt where rates reached 37/M.

In Israel, incidence trends of childhood Hodgkin lymphoma are steady along the 36 years examined where rates are higher in male (rate ratio of 2 in Jews and 1.25 in Arabs). For the Jewish population incidence rates were 10 to 12/M compared with 6/M on average for Arabs. The relative burden of the disease was 6% of all childhood cancers and was observed to be steady along the period.

Non-Hodgkin lymphoma (NHL) share in the total childhood malignancies decreased quite sharply from 1970 to 2005 where its share was 18% of all malignancies to reach 13% at the end of the period. In the Jewish population incidence rate of NHL decreased mostly in male from 35/M to reach a steady rate of 20/M from 1990 and on. The decline was sharper in female where incidence rate were 3/M in the 70s and halved (1.5/M) in mid-90s to reach the same level of Jewish male in early 2000s. In the Arab population rates were lower and steady around 1/M throughout the period. The decrease in incidence in the Jewish population is of particular interest as adult NHL rates presented a mirror trends, that is, more than doubled in the corresponding period.

Conclusions: The incidence of lymphomas in MECC countries including Israel is generally high, compared with Europe and the US SEER population. Hodgkin lymphoma's incidence rate is steady whereas a decrease was noted in NHL. Marked differences were noted with sex only in the Jewish population in Israel. Decreasing rate of NHL in Jews is opposed to trends in the adult population observed in Israel and in other countries and deserves further investigation.

New Horizons in the Chemotherapy Treatment of Childhood Cancers

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Improving overall survival and reducing morbidity are the major goals of childhood cancer management. Sustained improvements in pediatric cancer therapy are partly due to large randomized and nonrandomized studies being conducted by multidisciplinary cooperative groups. Theoretic concepts of chemotherapy, improved knowledge of pharmacokinetics and pharmacodynamics, and the drug resistance of current and new drugs enable a more rational approach to multiagent therapy. The adoption of aggressive, multiagent, short-course therapy has markedly improved outcomes, especially in lymphoma. The LMB/FAB protocol for children with Burkitt lymphoma shows that even decreasing doses do not affect overall survival and diminish the late effects of treatment, especially sterility, cardiomyopathy, and second malignancy. The remarkable progress achieved in pediatric Hodgkin disease is a tribute to this influential pioneer who served as a role model for many. Combined modality therapy, using low-dose, involved-field radiation and multiagent chemotherapy, results in a 5-year relative survival rate of more than 90% in children with Hodgkin disease. The use of new noninvasive staging techniques in lymphoma, including 18F-fluorodeoxyglucose-positron emission tomography, contributes to better defining of risk groups and segregates low-risk, intermediate-risk, and high-risk groups on the basis of a prognostic index, facilitating risk-adapted therapy. In recent years, progress to avoid late effects of treatment in brain tumors has been achieved by the combination of chemotherapy and lower doses of craniospinal radiotherapy in standard risk medulloblastoma. High-dose chemotherapy in infants with brain tumors was initiated to delay radiotherapy, with some success. Another new concept is maintenance chemotherapy in solid tumors; the European Pediatric Soft Tissue Sarcoma Group is studying the use of low-dose chemotherapy after more aggressive therapy in high-risk rhabdomyosarcoma. The new, international protocol, Euramos, for children with nonmetastatic osteogenic sarcoma, is studying the addition of interferon in the treatment of minimal residual disease. In addition, the development of protective drugs, such as the cardioprotector, dexzarexane, may allow the avoidance of late effects of chemotherapy and increased doses, if necessary. The need for clinical trials in children has been increasingly recognized by the scientific community and the broader public, leading to new legislation in some countries making intervention trials mandatory in children and adults before drug approval is given. Many new techniques, such as gene therapy, angiogenesis inhibitors, immunotherapy, and others that have not been part of the classic approach in pediatric oncology are now in clinical trials in the hope that they will influence the survival of these patients. For example, in newly diagnosed children with acute myeloid leukemia, the new CD33-targeted drug, gemtuzumab ozogamicin (Myelotarg), is being evaluated in combination with intensive induction chemotherapy. Chemotherapy protocols should be designed to maximize survival and minimize long-term toxicity. Improvements in the curing of children with cancer owe much to the culture of collaboration and multi-institutional clinical studies on which pediatric oncology is based.

Introduction to Targeted Therapies

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The improved knowledge of cancer biology represents a promising approach to more specific treatment options such as targeted therapy. Targeted therapy aims to selectively kill cancer cells. This selectivity is

based on molecules that are limited to cancer cells or carcinogenesis and tumor growth. Such selectivity of targeted therapies might lead to a more effective cancer treatment with less toxicity to normal cells. Targeted cancer therapies include several types of drugs:

1. Small Molecule Agents: such as protein tyrosine kinases, have proven to be good targets for small-molecule inhibitors that compete with ATP and inhibit kinase activity, which prevents activation of, and signal transduction from, the receptor. Novel small molecule inhibitors can occupy virtually any 3-dimensional surface on a target molecule, which lets them to be more specific for cancer treatment.

2. Monoclonal Antibodies: act by recognizing the protein of a single clone on the surface of the cell and then lock onto it. As a result these molecules recognize only one antigen and induce an immunologic response on the target cell which is the cancer cell. Another strategy for antitumor therapy is to target the receptors of growth factors like EGF and VEGF.

3. Nucleic Acid-based Agents: as nucleic acid molecules have a specificity assigned by Watson-Crick base-pairing, antisense technology allows rational drug design on the basis of the sequence, charge, and conformation of the molecular target. These agents have the potential for inhibiting expression of virtually any gene. Their efficacy is dependent upon their ability to bind their RNA substrate and suppress expression to protein.

It is very clear that targeted therapy requires careful selection of cancer patients whose malignant tumor expresses the given target in at least a small proportion of the cell population. Several of these recently identified targeted therapy agents have begun evaluation in clinical trials. Further development of these new agents in clinical trials, will be needed to improve survival and quality of life for patients.

Lymphoma in Mediterranean Countries

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The term lymphoma encompasses a diverse group of neoplasms with the common character of originating from the cells of the lympho-poietic system. Modern classifications of lympho-hemopoietic malignancies include lymphomas, leukemias, and multiple myeloma as 1 group of malignant diseases. In the World Health Organization classification, 2 main types of lymphomas are distinguished: Hodgkin lymphoma and non-Hodgkin lymphoma (NHL). The latter are distinguished between T-cell and B-cell lymphoma, which include chronic lymphocytic leukemia and multiple myeloma. However, most epidemiologic data do not yet follow the modern clinical-pathologic classification of NHL.

The IARC Globocan project includes estimates of the rates and number of NHL for different countries. These data are based on different sources. With respect to Mediterranean countries, data for Cyprus, Israel, and Jordan are derived from national cancer registration, data for Turkey, Tunisia, Algeria, and Lebanon are extrapolations from regional cancer registries, data for Egypt and Syria are estimates from frequency data, whereas data from Morocco and Libya are averages from neighboring countries.

The estimated incidence rates of NHL/100,000 in Mediterranean countries are reported in Table 1. The incidence was highest in Israel, intermediate in Jordan, Lebanon, Syria, and Cyprus, and low in the remaining countries. The analysis of age-specific rates showed in all countries but Israel an increase up to age 55, followed by a plateau, which might reflect a cohort effect. In Israel, rates increased up to age 80. In recent years, MECC has established cancer registries in Egypt and Jordan. A comparison of cancer registry and Globocan data for these 2 countries showed a good concordance for Jordan (age-standardized rates/100,000 in cancer registry 7.3 in men and 5.4 in women; in Globocan 6.8 and 5.7), whereas rates in Egypt was higher in the cancer registry (17.1 in men, 11.3 in women) than in Globocan (2.5 and 1.7). The analysis of specific NHL subtypes suggested a higher proportion of diffuse large B-cell lymphoma in Egypt than in the other countries, but the variable proportion of unspecified NHL makes the comparison difficult.

In conclusion, the analysis of descriptive epidemiology data of lymphoma in Mediterranean countries showed some important geographic differences, and stressed the need for caution in the interpretation of estimates based on limited data, as in the case of Globocan data for Egypt, which grossly underestimated the true incidence of NHL. These data demonstrate the need for etiologic studies of NHL in this region.

TABLE 1. Incidence Rates of NHL in Mediterranean Countries (Globocan Estimates)

Country	Men	Women
Morocco	5.3	3.5
Algeria	5.0	3.4
Tunisia	5.9	3.7
Libya	4.2	2.2
Egypt	2.5	1.7
Israel	14.0	11.7
Jordan	6.8	5.7
Lebanon	8.6	4.5
Syria	7.7	7.8
Turkey	3.8	3.1
Cyprus	10.4	6.7

Hodgkin's Lymphoma in Turkey

Munevver Buyukpamukcu, on behalf of the Turkish Society of Pediatric Oncology Group. *Faculty of Medicine, Department of Pediatric Oncology, Hacettepe University, Ankara, Turkey*.

Although Hodgkin disease (HD) is one of the common malignancies in childhood, there is limited information from developing countries. There are geographical variations in the epidemiologic features and clinicopathologic characteristics of HL in children from developed and developing countries. The aim of this presentation is to give epidemiologic features and treatment results of 1823 children with HD from a developing country. We collected the patients coming from all the pediatric oncology centers around the country. Our experience with the patients with cancer, approximately 25% of childhood malignancies, are lympomas, 40% of which are HD. All children seen were younger than 18 years old with biopsy-proven HD. Initial presentation of disease was supradiaphramatic in 75.5% and the cervical lymph nodes region was the most common location. Approximately half of the patients (51.2%) were in stages I to II. The median age of our series was lower (8 y) than in developed countries and mixed cellularity (MC) subtype predominant histologic type (46.5%). MC subtype predominancy may explain some viral infections, such as the Eptein-Barr virus, seen at high frequency in our country. A high incidence of Burkitt lymphoma in Turkey also suggests that Eptein-Barr virus may be a cofactor in the pathogenesis of both lymphomas in young children. There is a high incidence of males (M/F = 2.54). During the last 3 decades, our patients have had combined treatment modality as chemotherapy + radiatherapy (64.8%); 30.6% had chemotherapy alone. Chemotherapy protocols are mainly MOOP and ABVD according to the literature. The radiotherapy field is mainly involved (71%). In the last decade, patients with stages I to II disease received 3 to 4 cycles of combined chemotherapy and low dose involved-field radiotherapy. There were a total of 1823 patients from 22 centers in the country; overall survival was 63% in 1 center, 83% in 3 centers, and 90% to 100% in other centers. We found some prognostic factors for our patients that include stage, histology, age, lactic dehydrogenase, erythrocyte sedimentation rate, B symptoms, and chemotherapeutic regimens.

Conclusions: Turkish children showed type 1 Hodgkin lymphoma. Our centers' treatment results are the same as other centers in developed countries. We should have a national HL protocol which must be risk and sex adapted. Further studies on environmental and viral factors and molecular changes are needed. Finally, we should also have a late effects study protocol for our patients with HL.

1997-2002 Childhood Cancer Incidence in Izmir, Turkey

Sultan Eser. *Izmir Cancer Registry, Turkey*.

Aim: The aim of this presentation is to demonstrate the childhood cancer incidence in Izmir for the years 1997 to 2002.

Methods: Izmir Cancer Registry is a generalized population-based registry that covers the population of Izmir province since 1992. The population of the province is 3.37 million (2000 census), making Izmir the third largest city in Turkey (68 million). Although 9.9% of the population is 60 and over age group, 1.85% of the population comprises under 15. Izmir locates at the extreme west and one of the most developed region of the country.

Results: Total case number of under 15 is 607 (338 boys, 269 girls). 1.7% of all cancer cases among men and 2% of all cases among female pertain to under 15. For under 15, the calculated crude incidence rate is 131.1, ASR (world standard population) is 135.6 per million. Age specific rates are 139, 176.4, 121.8, and 106.5 per million, respectively, for 0, 1 to 4, 5 to 9, and 10 to 14 age groups. At the first row there are leukemias (30%) as usual, central nervous system (CNS) tumors are at the second row (21%), and lymphomas (15%) rank after CNS tumors at third row (Table 1).

TABLE 1. Annual Rates and Relative Frequency of the Childhood Cancers, Izmir 1997-2002

Site	Relative Frequency (%)	Incidence Rates (Per Million)	
		Crude Rate	ASR
Leukemia myeloperoxidase/ myelodysplasia	30.6	40.2	42.7
Lymphoid leukemia	22.9	30	31.9
Acute myeloid leukemia	5.8	7.6	8.2
Lymphomas reticuloendothelial	15.0	19.7	18.9
Hodgkin lymphoma	4.6	6	5.5
NHL (not Burkitt)	6.6	8.6	8.3
Burkitt lymphoma	2.1	2.8	2.8
CNS intracranial/spinal	21.3	27.9	28.2
Neuroblastoma.Per.Nerv.Cell	7.1	9.3	11.1
Retinoblastoma	2.6	3.5	4.1
Renal tumor	3.1	4.1	4.7
Hepatic tumor	1.2	1.5	1.9
Malignant bone tumor	4.4	5.8	5.0
Soft tissue extraosseous sarcoma	5.8	7.6	7.9
Germ cell trophoblast gonad	4.0	5.2	5.4
Malignant epithelial/melanoma	4.3	5.6	4.9
Other/unspecified malignant neoplasm	0.7	0.9	0.8
Total	100	131.1	135.6

ASR indicates Age Standardized Rate. World standard population.

Discussion: In the Western countries 1 of 14 and in less developed countries 1 of 7 of the cancer cases occurring under 45 have seen in children; this proportion is 1/10 in Izmir. Brain tumors are more common in more developed countries and have higher incidence than lymphomas. Lymphomas (especially Burkitt lymphoma) and retinoblastoma have higher incidences compared with apparently low brain tumor incidence in developing countries. Kaposi sarcoma related to HIV infection has a very high incidence in Sub-Saharan Africa. In Izmir at the previous (before 1997) series, lymphomas were at the second rank as in the most of developing countries. The rank shifting between lymphomas and CNS tumors is striking at 1997 to 2002 series.

Conclusions: We see that the childhood cancer patterns of Izmir mostly resembles the Western population's henceforth. Besides the ranking, the total and site-specific incidence rates are very close to the rates in developed countries: high incidence rates for CNS tumors, low incidence rates for non-Hodgkin lymphomas and retinoblastoma.

The Story of Establishment of Al-Malath Hospice in Jordan

Rana Hammad. *Al-Malath Foundation for Humanistic Care*.

On October 9, 1992 the Jordanian nation lived a very special day. All Jordanians gathered around their TV sets watching a 16-hour Telethon as part of a National Campaign to raise funds to build "Al-Amal (The Hope) Center for Cancer Cure." This Telethon attracted the interest and support of all Jordanians and instilled a feeling of pride and raised public awareness on the importance of fighting cancer with the best medical infrastructure and support system available. This event, however, served as an awakening call to consider the neglected needs of incurable patients who cannot be admitted into such cure oriented centers.

Although this need was recognized in Jordan for a while, it was not realized until a group of interested Jordanian professionals started meeting to explore the needs of the terminally ill and their families. And to consider the relevance and appropriateness of developing a program to meet those needs.

At that time, the scarce resources for cancer care in Jordan were only allocated to curative treatment, with no institutions, programs, or any health care resources where patients of incurable cancers and their families could seek support when curative care was no longer possible. Further there was no structure for support of health care professionals to deal with compounded grief of dying patients and family members.

The feasibility study pointed at the prevailing status of dissatisfaction with the health care provided to terminally ill patients, as opposed to the help they actually needed and presented demonstrable evidence that terminally ill patients can be made more comfortable without incurring any greater costs. Whereas on the other hand, optimistically pointed at a growing interest and some individually developed expertise, which needed to be coordinated and guided to help develop palliative care services and a national awareness of its importance.

In February 1993, our vision to make a difference was realized by the establishment "Al-Malath Foundation for Humanistic Care" as a Non-Governmental Organization and launching its Hospice program to be the first in its kind in Jordan and the Arab Countries.

Through a well-trained multidisciplinary health care team, Al-Malath Hospice provides palliative care for the terminally ill cancer patients and their family members at the comfort of their homes, addressing physical, psychologic, social, and spiritual needs. This is to include personal care, family support, control of pain and suffering, symptom control, emotional, spiritual, financial and legal support, and bereavement follow-up. All on a free of charge basis and a 24 hours, 7 days a week coverage.

Investing in the health care team rather than costly technology, the goal of care was and still is, to preserve the patient's dignity and enhance the quality rather than the quantity of remaining life. The goals of care also includes identification and treatment of suffering, improved communication between medical and nursing staff and patients and families and assurance that the care provided meets the needs and goals of patients. Also promoting integration and continuity of care as patients traverse hospital and homecare settings in the course illness.

Appreciating that being the only program in the country that provides care for patients in their final days; we are not only their final chance, but also their only choice. This was a burden to shoulder for 10 years till our team stretched a hand to "King Hussein Cancer Center" and developed the second palliative care program in the Kingdom. This collaborative work extended from January 2003 to August 2004 and resulting in a continuum of palliative inpatient and homecare services serving the population of patients who are treated at KHCC.

If A group of interested Jordanians who had a vague dream 14 years ago, managed through the years to pioneer a change and spearhead an awareness and commitment as to our moral and professional obligation to relieving suffering and improving quality of life. And if they managed—in total absence of resources and financial support—to change the terminal illness experiences of patients, their family members, and the society at large. Then any well-intended group at any spot in the world can induce even a larger influence, and change the face of suffering with only belief, will, and commitment.

The Middle East Cancer Consortium and Cancer Incidence Rates in the Region

Joe B. Harford. *National Cancer Institute, National Institutes of Health, US Department of Health and Human Services.*

In 1996, the Ministers of Health of Egypt, Israel, Jordan, Cyprus, and the Palestinian Authority (PA) signed an agreement to form the Middle East Cancer Consortium (MECC). Turkey joined the MECC in 2004. The overarching purpose of MECC is to reduce the burden of cancer in the Middle East through collaborative activities. The first major activity of MECC was to set up a Joint Cancer Registration Project, in which a population-based cancer registries would be created or enhanced in each jurisdiction, and cancer incidence data collected using consensus methodologies so as to allow comparison. The MECC-affiliated registries were in Nicosia, Cyprus; Tanta, Egypt; Jerusalem, Israel; Gaza City, PA Gaza; Beit Jalla, PA West Bank; and Izmir, Turkey. In addition to the common standards of registration, the staff of the MECC-affiliated registries participated in several joint training courses in cancer registration. Ten years after its establishment, MECC has published through the NCI a monograph entitled *Cancer Incidence in Four Member Countries* (*Cyprus, Egypt, Israel, and Jordan*) *of the MECC Compared with US SEER*. Individual chapters on various cancer sites were included in the monograph. These chapters highlighted not only the data itself but also research questions suggested by the data. A few of the major findings were

- Jordanians had the lowest overall incidence rates of cancer (all sites except nonmelanoma skin cancer); the US SEER population and Israeli Jews had substantially higher incidence, whereas Cypriots, Israeli Arabs, and Egyptians had intermediate incidence.
- Liver cancer incidence rates in Egyptians were more than 5 times higher than those of the other MECC populations, and more than 3 times that seen in the US SEER population. The high rates of liver cancer in Egypt is likely related to the higher prevalence of hepatitis B and C in Egypt.
- Egyptians and Israeli Jews had rates of non-Hodgkin lymphoma higher than in the US SEER population and considerably higher than in the other MECC populations.
- Childhood cancer incidence rates on the whole were less variable than adult cancer rates.

Other results can be found in the monograph itself, which is available on the MECC Web site at http://mecc.cancer.gov.

Hematologic Malignancies of Childhood

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Hematologic malignancies comprise the most common malignancies of childhood. They are diagnosed and classified using morphology, immunophenotyping (flow cytometry, immunohistochemistry), and cytogenetic and molecular genetic data. Although patients may present with solid tumors or leukemia, these distinctions are no longer used in lymphoid disease classification. Instead, because of biologic, genetic, and therapeutic similarities, lymphoblastic lymphomas (LBLs) are grouped with acute lymphoblastic leukemias as precursor B or T lymphoblastic disease, and Burkitt leukemia is grouped with Burkitt lymphoma. Lymphomas are separated into non-Hodgkin lymphoma (NHL) versus Hodgkin lymphoma (HL). NHL is further separated into T versus B disease. Subclassification of NHL is complex with multiple subtypes, but most subtypes are largely restricted to adults. Classic HL has 4 subtypes. Pediatric myeloid disease consists of acute myeloid leukemia (AML), smaller number of myelodysplastic syndrome (MDS) cases, and uncommon cases of juvenile myelomonocytic leukemia. AML is subclassified as de novo (DN−) or MDS-related (MDR−) AML. Although subgroups of MDS occur in adults, virtually all pediatric MDS is high-risk disease. Evaluation of hematologic malignancies requires a thorough history and physical, screening laboratory tests, and radiographic studies, but most importantly acquisition and proper processing of an adequate tissue sample of the malignant process. The sample must be obtained before delivery of any chemotherapy, including steroids, as subsequent necrosis may obstruct diagnosis. Surgical specimens must be examined quickly to avoid autolysis. When possible, an intact lymph node with capsule should be sampled. Air-dried touch preparations should be made, the sample sectioned at 2 mm intervals to facilitate fixation, samples taken for flow cytometry and genetic analysis, and samples placed quickly in fixative. Air-dried cytocentrifuge preparations or smears are made from body fluids and fine needle aspirates. All air-dried preparations, including marrow aspirate smears, are stained with a Romanowsky (eg, Wright-Giemsa) stain. Fixed Papanicolaou or hematoxylin and eosin-stained smears are of limited use for evaluation of hematologic malignancies. Surgical biopsy specimens, marrow particle preparations and biopsies, and cellblocks from body fluids and fine needle aspirates, are processed as surgical specimens with hematoxylin and eosin staining. Flow cytometric and cytogenetic analysis is recommended for new cases, excluding HL, with additional immunohistochemistry and genetic studies as indicated after initial review.

The common pediatric hematologic malignancies presenting as tumors are Burkitt lymphoma, LBL, large B-cell lymphoma (BCL), peripheral T-cell lymphoma (TCL) [most commonly anaplastic large cell lymphoma (ALCL)], and HL. Examples of each were used to illustrate critical diagnostic features, differential diagnosis, and use of ancillary laboratory studies.

The differential diagnosis of Burkitt lymphoma includes LBL, large BCL, and peripheral TCL. TCL is eliminated with immunophenotypic demonstration of B-cell derivation. Separation from large BCL requires attention to morphology (smaller regular cells in Burkitt lymphoma, with basophilic vacuolated cytoplasm in touch preparations), CD10 positivity (indicating follicular center origin), a very high (>95%) proliferative index (using MIB-1), TdT negativity to rule out LBL, and demonstration of Myc dysregulation by cytogenetic or fluorescent in situ hybridization analysis.

The differential diagnosis of LBL is Burkitt lymphoma and to a lesser extent other NHL. Keys to diagnosis are morphologic review, immunophenotyping, TdT positivity, and a high proliferative index value (but <95%).

Large BCL is diagnosed using morphology plus immunophenotyping to document B-cell clonality, eliminating both TCL and HL. TCL diagnosis is based on morphology, immunophenotypic exclusion of B-cell origin, identification of T antigen positivity with loss of other T antigens, and in anaplastic large cell lymphoma demonstration of CD30 positivity and usually Alk positivity. HL is diagnosed and classified using morphology, with confirmation of CD30 positivity and negativity for CD3, CD20, and CD45 in Reed-Sternberg cells.

Acute leukemia diagnosis is based on morphologic and flow immunophenotypic assessment of marrow blasts to identify precursor B, precursor T, or myeloid derivation. Precursor B acute lymphoblastic leukemias may be subclassified using genetic abnormalities into good, intermediate, and poor-risk groups. AML subclassification is based on myelodysplastic features (MDS-related vs. de novo); further AML characterization requires cytogenetic and molecular genetic evaluation. MDS diagnosis is based on peripheral cytopenias, morphologic dysplasia, marrow blast percent, and characteristic cytogenetic abnormalities (eg, −7, 5q−, +8); pediatric MDS is inherently poor-risk disease. Finally, juvenile myelomonocytic leukemia is characterized by shared features with MDS, leukocytosis with immature forms, monocytosis, hepatosplenomegaly, elevated hemoglobin F, and GM-CSF hypersensitivity in marrow progenitors.

Molecular Pathology of the Histiocytoses

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There are 2 major types of histiocytes and, consequently, 2 major types of histiocytoses: (A) dendritic cell-related disorders of which Langerhans cell histiocytosis, previously called histiocytosis X, is the most common and (B) macrophage-related disorders of which hemophagocytic lymphohistiocytosis (HLH) is the most common. So far, relevant pathologic molecular findings are mainly associated with HLH, which therefore will be the focus here.

HLH is a rare disease with high mortality, most commonly characterized by fever, hepatosplenomegaly and cytopenias. It comes in 2 forms, familial HLH (FHL) and secondary HLH that may be difficult to distinguish. The HLH diagnosis is based either on a positive family history, evidence of mutations associated with HLH, or that 5 out of 8 diagnostic criteria are fulfilled. These 8 criteria include the 5 initial criteria fever, splenomegaly, bicytopenia, hypertriglyceridemia or

hypofibrinogenemia, and hemophagocytosis. The 3 additional criteria are low/absent natural killer-cell activity, hyperferritinemia, and elevated sIL-2 receptor levels (CD25). Secondary forms of HLH include, among others, malignancy-associated HLH, virus-associated HLH (most commonly EBV), bacteria-associated HLH, and macrophage-activating syndrome.

The estimated incidence (in Sweden) of the familial form is 1 in 50,000 live births and it occurs most frequently among young children, especially during the first year of age. Clinical studies have resulted in a markedly improved survival of HLH, from being a rapidly fatal disease the long-term cure rate is now around 50% with the HLH-94 treatment protocol (Henter et al, 2002). It has been shown that FHL is associated with a dysfunctional immune response including low cytotoxic capacity (Perez et al, J Pediatr 1984) and that the symptoms are associated with high levels of inflammatory cytokines (Henter et al, Blood 1991). In addition, a mononuclear leukocyte cell accumulation is evident.

Thus, 2 remaining key questions were which are the cellular and the molecular mechanisms causing FHL, respectively. In 1996 it was suggested that the underlying deficiency could be a defect in programmed cell death (Henter et al, Med Pediatr Oncol 1996). Subsequently, it was shown that lymphocytes from FHL patients have intact Fas-triggered apoptosis and intact Etoposide-triggered apoptosis, but a deficiency in spontaneous triggering of apoptosis suggested to be due to either a defect in the Fas/Fas-Ligand system or the perforin-granzyme B pathway (Fadeel et al, Br J Haematol 1999).

Now mutations in 3 genes (*PRF1*, *UNC13D*, and *STX11*) have been associated with FHL encoding the proteins perforin, Munc13-4, and syntaxin-11, respectively (Stepp et al, Science 1999; Feldmann et al, Cell 2003; zur Stadt U et al, Hum Mol Genet 2005). Whereas perforin is essential for the apoptotic process per se, Munc13-4 is essential for priming the cytolytic perforin-containing vesicles for fusion with the plasma membrane. Interestingly, Munc13-4 acts together with the protein encoded by the gene *Rab27a*, which main function is tethering of the vesicles to the plasma membrane. Mutations in *Rab27a* cause Griscelli syndrome type 2. The cellular function for syntaxin-11 remains to be fully elucidated, but it seems as if *SXT11* mutations may result in a clinical picture that may be milder than those caused by mutations in the genes *PRF1* and *UNC13D*.

In sum, the clinical, cellular, and molecular studies of FHL patients have resulted in a markedly improved survival as well as improved understanding of human immune biology, and this is one of the success stories in pediatric hematology-oncology of the last decade.

Childhood Cancer in Egypt: Results of Population-based Cancer Registry in Gharbiah, Egypt, 2000-2002

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Introduction: Until very recently, Egypt was lacking population-based cancer registries. Hospital-based registries were available in many centers; the largest was the series of the National Cancer Institute, Cairo University. Nonetheless, it was not possible to get incidence data neither on the national or regional level. With the establishment of MECC population-based cancer registry in Gharbiah in the middle of Nile delta, it became possible to have incidence data for a district in Egypt that could be generalized to the national level. The present paper outlines the methodology used and incidence data on childhood cancer and discusses possibility of extrapolation on the national level.

Materials and Methods: The Gharbiah population-based cancer registry was established in 1999 as a part of the Joint Registration Project of the Middle East Cancer Consortium. It is located in the Middle of the Nile delta, in Tanta Cancer Center of the Ministry of Health (MoH), Egypt. It is jointly sponsored by MOH and National Cancer Institute, Bethesda through MECC. Data collection is active covering all sources of data related to incident cancer cases both within and outside Gharbiah including death certificates. The registry follows MECC standardized methodology with regular auditing, both internal and external, to guarantee high-quality data. Having number of incident cases and age and sex distribution of Gharbiah population allows the calculation of incidence rates and their standardization for world population (ASIR) for comparative purposes. The current paper describes results related to pediatric cancer, below the age of 15 years for the years 2000 to 2002.

Results: During the study period, the number of incident childhood cancer cases was 460, representing 4.4% of incident cases in all ages (10,440 cases). The male:female ratio was 1.6:1 (283 males and 177 females). The national incidence rate was about 4000 new cases. On the basis of an average survival of 2.5 years, the prevalence could be around 10,000 cases per year.

As shown in Table 1, lymphomas, leukemias, and CNS and intracranial malignancies accounted for about 2/3 of childhood cancers. Each of other sites accounted for $< 10\%$ of childhood cancer cases. One hundred thirty-two cases were lymphomas (28.7%). Hodgkin lymphoma represented 36.4% of these cases. The remaining 63.6% was non-Hodgkin lymphoma. The majority was nodal (73.8%) compared with 26.3% as extranodal disease. The ASIR (world) of malignant lymphoma in Egypt is one of the highest rates worldwide (37.7/1,000,000). The rate for US SEER was 13.5/1,000,000. The highest rate reported in MECC registries was that of Israeli Arabs (24.4/1,000,000).

Burkett lymphoma represented 35.9% of cases, followed by lymphoblastic lymphoma (23.1%) and NHL, diffuse large cell (15.3%). All other pathologic types accounted for 25.7% of cases. Stage was reported in 84.8% of cases. Localized and regional disease was reported for 49.9%. Stage was distant in 54.1%.

Discussion: The results mentioned are based on Gharbiah govern orate. To evaluate if Gharbiah could be used to get national estimate, the Human Development Index (HDI) was used. The HDI is a composite index commonly used as an indicator of degree of development. The HDI for Egypt was 0.687. The median of all govern orates was 0.685. PDI of Gharbiah was 0.689, very close to the median. We can safely say that results of Gharbiah are a fair estimate of the entire country waiting for the establishment of more population-based cancer registries.

Conclusions:

(1) The burden of childhood cancer in Egypt is serious.
(2) Lymphomas specially NHL is very special in Egypt and needs further research.
(3) Palliative care of children with cancer is needed in all stages of the disease.

TABLE 1. Site Distribution of Childhood Cancer (460 Cases), Gharbiah Population-based Cancer Registry, 2000-2002

Site	Frequency (%)
Lymphoma and reticuloendothelial system	28.7
Leukemias	24.3
CNS and intracranial malignancies	10.9
Sympathetic nervous system	7.0
Malignant bone tumors	6.1
Soft tissue sarcomas	5.6
Renal tumors	3.9
Gonadal neoplasms	2.2
Retinoblastoma	2.0
Hepatic tumors	1.3
Other malignancies and NOS	8.0

"Genetic Epidemiology Studies Based on Treatments—Where We Are?"

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Cancer may be defined as a genetic disease of the somatic cell. All cancers contain multiple acquired genetic abnormalities. Indeed each specific cancer may be divided to several genetic subtypes that may be defined by rather specific epidemiologic characteristics, clinical and pathologic presentations, response to therapy, and prognosis. During the talk, I reviewed several clinical relevant aspects of molecular genetics of leukemia: diagnostics; clues to etiology; significance in response to therapy.

A. Which Genetic Subtypes Should We Diagnose? It is important to remember that *treatment is the most important prognostic factor*. Therefore, the prognostic significance of a specific genetic abnormality

depends on the therapeutic protocol. For example, the translocation that fuses the gene E2A on chromosome 19 with PBX1 on chromosome 1 has been first discovered as a bad prognostic factor in childhood acute lymphoblastic leukemia (ALL) but lost its bad prognostic impact in modern more intensive therapeutic protocols. Currently, the translocations BCR-ABL, MLL-AF4, and hypodiploidy are bad prognostic factors and the presence of hyperdiploidy or TEL-AML1 are good prognostic factors in childhood ALL.[1]

B. Which Diagnostic Methodologies Are Used? Some methodologies are directed toward the identification of a specific abnormality—for example, RT-PCR to detect a fusion gene. Others are more general and hence may detect new or associated abnormalities—for example, cytogenetic analysis or DNA microarrays.

C. Clues to Etiology: The existence of specific genetic abnormalities that can be detected by extremely sensitive methodologies such as PCR led to the discovery of the clonigenic genetic abnormalities at the neonatal blood spots of children with leukemia. This finding has substantiated Greaves hypothesis that childhood leukemias develop in 2 stages. Most of the known structural and numerical chromosomal abnormalities such as hyperdiploidy or the TELAML1 translocation occur before birth and induce the proliferation of a premalignant clone. This event is necessary but insufficient for the development of leukemia. At least one additional postnatal genetic event must be acquired for the development of leukemia.[2]

D. Early Diagnosis? These findings have raised the opportunity of neonatal screening for leukemia-associated genetic events to identify children at high risk for leukemia. However, pilot screens in umbilical cord blood have revealed that these events, for example, the TEL-AML1 translocation, are quite common. About 99% of the neonates who have circulating blood cells with premalignant genetic abnormalities will never develop leukemia, hence such screening is futile.[2]

E. Genetic Epidemiology: Epidemiologic studies of leukemia has revealed a high prevalence of hyperdiploid and TEL-AML1 B cell precursor (''common'') ALL in preschool children in the wealthy suburban population. One popular theory suggests that this leukemias are facilitated by a rare immune response to common infections that are delayed beyond the neonatal period in modern more effluent communities with relatively few children per 2 family.[2] We have recently observed a strong interferon response gene expression signatures in these leukemias providing a biologic support for that theory.[3]

F. Lessons From Genetic Syndromes: Association between genetic syndromes and cancers have revealed multiple genes and pathways that are also important for the evolution of sporadic cancers. The study of the leukemias of Down syndrome have revealed important clues on the role of extrachromosome 21 in leukemogenesis and has served as an prime model of cooperating prenatal and postnatal mutations in the evolution of childhood leukemia.[4]

G. Genetic Modifier of Response to Therapy: Polymorphic alleles of genes coding enzymes and other modifiers of activity of anticancer drugs may have profound effects on the outcome to therapy. For example, TPMT is an enzyme that catabolize the drug 6MP. A rare weak allele of TPMT is associated with marked accumulation of the active drug and severe, life threatening, bone marrow suppression. Recently, it has been shown that heterozygous children for this allele (about 10% of all patients) have a better response to antileukemic therapy with 6MP.[5] However, heterozygosity to TPMT also confer increased risk to secondary cancers in patients receiving higher dose of 6MP with cranial irradiation.[6] With better diagnostic genomic tools a vast array of genetic abnormalities in cancer are being diagnosed. Their prognostic and diagnostic significance strongly depends on the specific treatment protocol. Like many things in life—everything depends on the context!

References:

1. Pui CH, Relling MV, Downing JR. Acute lymphoblastic leukemia. *N Engl J Med*. 2004;350:1535–1548.
2. Greaves M. Infection, immune responses and the aetiology of childhood leukaemia. *Nat Rev Cancer*. 2006;6:193–203.
3. Einav U, et al. Gene expression analysis reveals a strong signature of an interferon-induced pathway in childhood lymphoblastic leukemia as well as in breast and ovarian cancer. *Oncogene*. 2005;24:6367–6375.
4. Izraeli S. Perspective: chromosomal aneuploidy in leukemia—lessons from Down syndrome. *Hematol Oncol*. 2006;24:3–6.
5. Stanulla M, et al. Thiopurine methyltransferase (TPMT) genotype and early treatment response to mercaptopurine in childhood acute lymphoblastic leukemia. *JAMA*. 2005;293:1485–1489.
6. Relling MV, et al. Etoposide and antimetabolite pharmacology in patients who develop secondary acute myeloid leukemia. *Leukemia*. 1998;12:346–352.

What to Do for Patients With Recurrent ALL?

Barton A. Kamen. *Cancer Institute of New Jersey, Robert Wood Johnson Medical School, New Brunswick, NJ.*

Acute lymphoblastic Leukemia (ALL) in children presents several interrelated problems to the pediatric oncologist. Even though the cure rate has soared upward during the past several decades, the prevalence of the disease (25% to 30% of all pediatric cancer) and a 20% recurrence rate still means that patients with relapsed ALL represent one of the most common malignancies (ie, 20% of 30% is 6% which is in the same range of the common solid tumors such as Wilms, rhabdomyosarcoma, neuroblastoma, Ewing's, and osteosarcoma). Moreover, we are just learning the price (late effects) of our curative regimens and in doing so, have attempted to develop *risk-based therapies* to minimize them. The risk to the patient is undertreatment as salvage therapy; especially for children relapsing while still on therapy is poor.

To develop rationale approaches we suggested finding answers to the adverb answer such questions as How?, When?, Where?, In what way?, or How often? Can we find a unique identifier, a marker that is also a target for therapy such as bcr-abl in some forms of chronic myelogenous leukemia. The heterogeneity of ALL is such that the magic bullet, that is, a specific drug with great specificity and little toxicity has not emerged. The increases in the cure rate have come from empirically based clinical trials using drugs were developed before 1960 (primarily vincristine, asparaginase, prednisone, methotrexate, 6-mercaptopurine, and Adriamycin). New classes of drugs, or even new drugs as analogs of existing ones have not yet found a way into the mainstream (perhaps dexamethasone for prednisone, but the increased orthopedic toxicity remains an issue).

Are there any agents on the horizon? In broad-brush strokes, we can think of immunotoxins against unique antigens, inhibitors of signaling pathways, or analogs of existing agents because the last group has served us well for so many decades. From a B-lineage view, CD19 and CD20 may be targets. T-lineage targets may be CD25 (IL 2 receptor), CD7, and CD3. More general targets could include CD52, CD33, and Her-2/Neu. ''Avant Garde'' pathways that may be upstream in the parade/cascade of pathways leading to cell proliferation or the loss of control of apoptosis includes: mTOR (mammalian target of rapamycin), Notch and Wnt and perhaps Neprilysin (CALLA, CD 10, neutral endopeptidase), a known suppressor gene. mTOR resides at a critical junction of grow, no grow, and general well metabolic health of a cell. Drugs such as rapamycin and more recently, analogs are finding their way into oncology in addition to its well-defined use for graft versus host and organ rejection. As learned from a developmental biology view, Notch and Wnt offer potentially useful targets. Last year, in this Journal we briefly reviewed the potential for CD10 to be investigated initially from a prognosis view but also as a target. CD10 is a relatively ubiquitous integral membrane protein that has a broad specificity including signaling molecules and growth factors. CD10 acts to inhibit cell growth by degrading the ligand. Conversely, casein kinase II (protein kinase II) phosphorylates CD10 and inactivates it. It is not surprising that casein kinase II is an oncogene. Even though CD10 positivity has been a marker for more than 30 years, distinguishing active from inactive (phosphorylated) forms has never been done. Even quantitating enzyme activity in ALL samples has not been reported. Intuitively, it would seem important to know whether the antigen we measure was active or not. For example, if there was too much casein kinase II, CD10 could be inactive, therefore, a strategy could be to inactivate the kinase. Similarly, maybe mutant (polymorphisms?) of CD10 need to be identified to serve as a better prognostic marker.

Finally, we need to consider if there are any new models of time proven drugs that might yield advantages in efficacy. Because 80% of the patients are cured with conventional cytotoxic agents, some of the last 20% could be ''pharmacologic failures'' associated with CADEM: compliance, absorption, distribution, excretion, and metabolism. Dexamethasone may have some advantages over prednisone 6TG did

not make major differences compared with 6MP and we are studying the feasibility of using aminopterin to replace methotrexate based on some pharmacodynamic parameters. Genetic polymorphisms concerned with 6MP, folate, and multidrug resistance may also play a role in success or failure (or toxicity) of our generally successful therapy.

The Biochemistry and Pharmacology of Neurotoxicity Seen in Patients Treated for ALL

Barton A. Kamen and Peter Cole. *Cancer Institute of New Jersey, Robert Wood Johnson Medical School, New Brunswick, NJ.*

In general, late effects for children cured of a cancer will be experienced by 30% to 50% of the patients. In particular, as the cure rate for children with ALL has increased over the last $\frac{1}{2}$ century, the price of the cure as measured in late effects is becoming more evident. Orthopedic difficulties (osteoporosis or avascular necrosis), heart failure, reproductive and hormonal failure, and neurocognitive problems related to therapy are becoming more prominent, to name just a few major organ sites. The toll that therapy-related toxicity can have is such that as the cure rate has increased, there are greater efforts being made to develop prognostic markers to develop risk-based therapy that might spare some patients of un-needed therapy and hence some potential toxicity. The "down" side of such tactics is that if treatment fails, then retreatment will be more aggressive and, therefore, potentially more toxic. The risks of "risk-based therapy" are, therefore, significant. However, if the prognostic markers are very sound and the therapy adequate, then the goal of maintaining the cure with minimal risks will be attained. Another approach to minimize toxicity is to more completely understand it so as develop preventive or therapeutic interventions that will not interfere with curative intent. Because approximately 80% of children with ALL have curative disease using drugs that are time proven (all used or developed before 1960), the possibility of understanding pharmacogenetic, pharmacokinetic, and pharmacodynamic differences between patients may allow increased efficacy of known drugs. With specific regard to neurotoxicity seen in patients with ALL, offending agents include: radiation therapy, steroids, antifolates, and nucleoside analogs. In recent years, the need to use any radiation therapy for the majority of children is declining. The agents, therefore, most likely to be causative of neurocognitive dysfunction are the chemotherapeutic drugs and in particular, the folate analog, methotrexate. There are intuitive reasons for assuming that methotrexate is one of the culprits. It comes from what is known about folate metabolism, inborn errors of folate metabolism, and genetic polymorphisms. During gestation, a folate deficiency induced by diet, by genetically engineered folate receptor knockouts or by antifolates are embryonic lethal or result in midline, neural tube defects. A folate deficiency will lead to hyperhomocysteinemia. Homocysteine is toxic to endothelium and as a glutamate analog, that is, an excitotoxic amino acid, directly toxic to the central nervous system. Because every time methotrexate is administered a patient may experience some degree of a "biochemical folate deficiency" the drug may be mimicking what we see in patients with poor diets or polymorphisms in folate-mediated pathways such as methylene tetrahydrofolate reductase polymorphisms, methyltetrahydrofolate transferase deficiency, or a formimino transferase deficiency. There have also been children with autoantibodies against the folate receptor who have very low cerebrospinal fluid folate and have seizures and autistic like qualities. A folate deficiency and/or increases in homocysteine have also been associated with Parkinson disease and Alzheimer disease. The physiology/biochemistry of folate and folate-mediated reactions is, therefore, very much intertwined with methotrexate pharmacology. A more complete understanding of these interactions has led us to postulate and develop protocols to minimize the neurocognitive toxicities that are being seen in patients with ALL. Specifically, the use of an NMDA antagonist such as dextromethorphan or memantine (the former has shown activity in amyotrophic lateral sclerosis patients and the latter is approved as an adjunct for treating patients with Alzheimer disease) might be protective or rescue patients treated with methotrexate. It is also known that methotrexate can increase adenosine content in the CSF and in inflammatory compartments. Adenosine is a potent neurotransmitter associated with somnolence and seizures. The use of an antagonist such as a methylxanthine may prove effective as already shown by several groups. Finally, the development of an antifolate that does not enter the brain may be useful to limit CNS toxicity, although it will be important to show that it does not decrease the cure rate. Such a drug may be aminopterin. We have shown that at equivalent systemic pharmacodynamics to methotrexate that aminopterin does not significantly get into brain of animals or CSF of patients. The potential value of this difference between methotrexate and aminopterin needs to be proven.

Nutrition During Cancer Treatment

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Pediatric cancer patients undergoing chemotherapy have considerably low energy and nutrition intakes that can cause malnutrition. Depending on diagnosis, stage, treatment, and socio-economic status, prevalence of malnutrition ranges from 8% to 60%.[1,2] Even the patients with standard-risk ALL may have malnutrition at diagnosis.[1] Chemotherapy and related problems may couple prevalence of malnutrition in short periods.[3] Malnutrition may alter pharmacokinetics of the drugs resulting in increased toxicity, and thus may affect response to treatment.[4] Malnourished children experience frequent dose adjustments and more chemotherapy delays.[5] Lower intakes of antioxidants (vitamins C, E, and β-carotene) are associated with increases in the adverse side effects of chemotherapy.[6] Nutritional status has no effect on the prognosis of ALL, however, improved survival has been shown in localized solid tumors in the past.[2,7]

There are some risk factors for malnutrition in patients with malignant disease. These can be categorized into 2 groups[8]: High-risk group includes patients with advanced stages during initial intensive treatment (unfavorable histology of Wilms tumor, neuroblastoma, rhabdomyosarcoma, Ewing sarcoma), some non-Hodgkin lymphomas, tumors of the head and neck, AML, poor prognosis ALLs, multiple relapse leukemias, high-grade CNS tumors, and stem cell transplantation. Patients with good prognosis ALL, nonmetastatic solid tumors, and advanced tumors in remission have low risk of malnutrition.

Several causes for malnutrition can be identified during cancer treatment. These are cachexia, gut toxicity due to antineoplastic agents, infections, treatment-related anemia, psychosocial problems, specifically depression, irradiation of the head, neck, and chest, and tumor location. Jaw pain due to vincristine, prolonged fastings due to diagnostic procedures, surgery type, ion inbalances, and muscle weakness may also contribute to the nutritional status. Treatment-related severe mucositis are common after high-dose chemotherapies whereas diarrhea is observed in one-forth of the patients.

Some drugs such as doxorubicin, methotrexate, cisplatinum, and cyclophosphamide can affect taste buds. In the oncology wards, parents and nurses identify eating problems and altered food choice during chemotherapy.[9] Eating problems may arise from altered taste, learned food aversions, nausea, vomiting, painful swallowing, loss of appetite, or other factors. Parents notice that their children usually choose "salty, spicy, and sour foods" during chemotherapy.[9]

Nutritional intervention is required either at diagnosis or during cancer treatment. The goals of nutritional support are to achieve and maintain desirable weight and to prevent or correct malnutrition. Nutritional issues require a good team work comprising of child, family, pediatrician, nurse, registered dietitian, gastroenterologist, and pediatric surgeon.

In daily practice a 3-day dietary recall using a nutrition diary, assessment of appetite and activity levels, history of GIT symptoms, and concomitant medications may help understand nutritional status of a child. Weight and height are the most used parameters in the nutritional evaluation rather than laboratory indices or detailed anthropometric measurements.[10] Using height and weight measurements, body mass index and ideal body weight can be calculated.[11]

Nutrition practice in pediatric oncology clinics can be improved using evidence-based nutrition protocols, as was recommended by St Jude Children's Research Hospital.[12] Estimated needs for nutritional elements must be calculated using ASPEN guidelines.[13]

Feeding routes are usually peroral or via tube in cancer patients. The latter can be achieved by either naso-gastric, naso-duodenal, naso-jejunal tubes, or gastrostomy devices. Oral intake can be improved by small frequent feedings, offering favorite nutritious foods during treatment-free periods, avoiding strong odors and sweet foods, offering salty and cool foods,

slow eatings, serving soft or pureed bland foods or liquids, and moistening foods. Tube feeding requires a pump and a set, a silicon tube and supplement products. This way makes continuous feeding possible at bedside or at home. Tube feeding via gastrostomy devices are also effective in good hands with minimal problems.[14–16]

Enteral way has some advantages over parenteral route in terms of better maintenance of structural and functional integrity of the GIT, decreased risk of bacterial translocation, more physiologic and efficient use of nutrients, decreased hepatobiliary complications, and cost-effectiveness.[5,14,17,18] Enteral feeding is also safe and effective in BMT patients.[19]

To conclude, pediatric cancer patients are candidates for malnutrition during their treatments. Children have to be monitorized properly, and early nutritional interventions may be needed in the follow-up.

References:

1. Reilly JJ, Weir J, McColl JH, et al. Prevalance of protein-energy malnutrition at diagnosis in children with acute lymphoblastic leukemia. *J Pediatr Gastroenterol Nutr*. 1999;29:194–197.
2. Donaldson SS, Wesley MN, DeWys WD, et al. A study of the nutritional status of pediatric cancer patients. *Am J Dis Child*. 1981;135:1107–1112.
3. Yarış N, Akyuz C, Coskun T, et al. Nutritional status of children with cancer and its effect on survival. *Turk J Pediatr*. 2002;44:35–39.
4. Sala A, Pencharz P, Barr RD. Children, cancer, and nutrition: a dynamic triangle in review. *Cancer*. 2004;100:677–687.
5. Andrassy RJ, Chwals WJ. Nutritional support of the pediatric oncology patient. *Nutrition*. 1998;14:124–129.
6. Kennedy DD, Tucker KL, Ladas ED, et al. Low intakes are associated with increases in adverse effects of chemotherapy in children with acute lymphoblastic leukemia. *Am J Clin Nutr*. 2004;79:1029–1036.
7. Weir J, Reilly JJ, McColl JH, et al. No evidence for an effect of nutritional status at diagnosis on prognosis in children with acute lymphoblastic leukemia. *J Pediatr Hematol Oncol*. 1998;20:534–538.
8. Mauer AM, Burgess JB, Donaldson SS, et al. Special nutritional needs of children with malignancies: a review. *J Parenter Enteral Nutr*. 1990;14:315–324.
9. Skolin I, Wahlin YB, Broman DA, et al. Altered food intake and taste perception in children with cancer after start of chemotherapy: perspectives of children, parents and nurses. *Support Care Cancer*. 2006;14:369–378.
10. Ladas EJ, Sacks N, Brophy P, et al. Standards of nutritional care in pediatric oncology: results from a nationwide survey on the standards of practice in pediatric oncology. A Children's Oncology Group Study. *Pediatr Blood Cancer*. 2006;46:339–344.
11. Barr RD, Gibson B. Nutritional status and cancer in childhood. *J Pediatr Hematol Oncol*. 2000;22:491–494.
12. Bowman LC, Williams R, Sanders M, et al. Algorithm for nutritional support: experience of the metabolic and infusion support service of St. Jude Children's Research Hospital. *Int J Cancer*. 1998;(suppl 11):76–80.
13. August D, Teitelbaum D, Albina J, et al. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. *J Parenter Enteral Nutr*. 2002;26:25SA–32SA.
14. Mathew P, Bowman L, Williams R, et al. Complications and effectiveness of gastrostomy feedings in pediatric cancer patients. *J Pediatr Hematol Oncol*. 1996;18:81–85.
15. Barron MA, Duncan DS, Gren GJ, et al. Efficacy and safety of radiologically placed gastrostomy tubes in pediatric haematology/oncology patients. *Med Pediatr Oncol*. 2000;34:177–182.
16. Ringwalg-Smith K, Hale G, Williams R, et al. Comparison of two different low-profile gastrostomy enteral feeding devices in pediatric oncology patients. *Nutr Clin Prac*. 2000;15:189–192.
17. Aquino VM, Smyrl CB, Hagg R. Enteral nutritional support by gastrostomy tube in children with cancer. *J Pediatr*. 1995;127:58–62.
18. Christensen ML, Hancock ML, Gattuso J, et al. Parenteral nutrition associated with increased rate in children with cancer. *Cancer*. 1993;72:2732–2738.
19. Seguy D, Berthon C, Micol JB, et al. Enteral feeding and early outcomes of patients undergoing allogeneic stem cell transplantation following myeloablative conditioning. *Transplantation*. 2006;82:835–839.

Febrile Neutropenia in Children

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Febrile neutropenia is one of the major acute side effects of intensive therapy in pediatric cancer, necessitating prompt initiation of empirical broad-spectrum antibiotics.

Patients may be classified according to the following risk factors as low or high risk.

- Duration of neutropenia (> 10 d)
- Depth of neutropenia (< 100/mm^3)
- Type of cancer (solid tumor, lymphoma, leukemia)
- State of disease (remission, progressive disease, recurrence)
- Bone marrow involvement
- Type of therapy (conventional, BMT/SCT)
- Additional health problems (respiratory, neurologic, etc.)

Generally the following are accepted as low risk

- Duration of neutropenia < 7 to 10 days
- Solid tumor, early stage non-Hodgkin lymphoma
- Leukemia in remission, in maintenance therapy
- No sepsis or sign/symptoms of documented severe infection
- No additional organ/system disorder
- Looking well

Initial evaluation of the febrile neutropenic child should include the history of the child, a detailed physical examination with particular attention to the skin, perioral, perirectal areas, blood culture (peripheral and catheter), urinalysis and culture, cultures of lesions and stool (if diarrhea), CBC, biochemistry. Chest x-ray, other imaging and other tests are done as necessary.

The standard of care in febrile neutropenic children is that they should be hospitalized and treated urgently with IV wide spectrum empiric antibiotics until fever subsides and ANC > 500/mm^3. Empiric therapy should be modified according to culture results and clinical situation.

Empiric antibiotherapy should have a wide spectrum (including *P. aeruginosa*), high bactericidal drug levels in serum, low toxicity, should be easy to administer. According to international guidelines treatment may begin as Monotherapy (Ceftazidime, imipenem, cefepime, meropenem, cefoperasone/sulbactam, piperacilin/tazobactam) or Duotherapy (an antipseudomonal beta-laktam + aminogli-coside or an antipseudomonal carboksipenicilin/ureidopenicilin + aminoglycoside). Generally glycopeptides (vancomisin/teicoplanin) should not be used for initial empirical therapy; they should be added according to culture results or clinical signs, unless there is severe mucositis, clinically overt severe catheter infections, colonization with *MRSA* or *Pneomococci* resistant to penicilin/cefalosporins or hypotension. Antifungal therapy is initiated empirically on 5 to 7 days if fever persists and no site of infection is detected or if there is clinical signs of or positive cultures for fungal infection. Colony stimulating factors (G-CSF) may be used as primary or secondary prophylaxis.

For low-risk patients, monotherapy is recommended. In our institutional studies, in solid tumors, monotherapy has been used since 1994 and was successful. Monotherapy trials consisted of ceftazidime, ceftazidime vs. cefoperazone-sulbactam (randomized = R) ± G-CSF; ceftazidime vs. Cefepime (R); and cefepime vs. Tazobactam (R). In 305 neutropenic episodes, the median duration of neutropenia was 6 days (2 to 46 d). Episodes with severe neutropenia (ANC < 100/mm^3) increased from 25% to 75% recently. Total success was 98% to 100%. Clinically documented infections ranged between 34% and 80% in different periods. Gram (−) isolates were dominant before 1998, Gram (+) isolates and fungal infections increased in recent periods. Considering modifications, aminoglycosides were added in about 25% of episodes in all periods.

Recently other options for low-risk patients with good compliance are starting with IV therapy and continuing with p.o. therapy or stopping therapy even before ANC > 500/mm^3 if WBC, ANC, platelet counts are rising or giving p.o. antibiotherapy (cefepime is the suggested one) from the beginning.

In Turkey, in children with cancer, approximately 2400 febrile neutropenic episodes are encountered annually. In a national prospective

study in the first 6 months of 2004, 829 febrile neutropenic episodes in 472 children with cancer in 24 pediatric hematology/oncology centers in Turkey were evaluated. Forty-nine percent of all episodes were documented clinically. Upper respiratory tract infections were most frequent. Thirty-two percent of all episodes were documented microbiologically. Twenty-one percent had bacteremia/fungemia. Ninety-three percent of the documented microorganisms were bacteria, (Gram+ bacteria were seen more frequently than Gram− bacteria), 6.4% were fungi and 0.4% were viruses. Pathogens were rarely isolated in throat and stool cultures, all in clinically documented cases, suggesting that routine throat and stool cultures are not indicated in the absence of clinical findings. These results form a basis for planning other multicentric studies and planning empirical treatment strategies.

We should remember that the success of more intensive treatment in childhood cancer is directly associated with advances in supportive care, including prompt and appropriate treatment of febrile neutropenia.

Hospital Resource Utilization in Pediatric Cancers: A Preliminary Study in a University Based Pediatric Oncology Center in Turkey

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Every year, more than 160,000 children are newly diagnosed with cancer. The real number of new cases is not known because many of the children with cancer are not registered in many countries. Despite groundbreaking advances in diagnosis and treatment of cancer, children with cancer who live in developing countries have less than a 50% survival rate, as opposed to 80% for children living in developed countries. Intensive chemotherapies, risk-based approaches in treatment, advances in surgery and radiotherapy, stem cell transplantation, developments in supportive and intensive care approaches are increasing the gaps between developed and developing world. We have to investigate the utilization of sources to overcome the problems. Regarding the hospital resource utilization, there is limited data from developed world although there is almost no data from developing world.

We previously investigated the reasons for hospitalization in 1811 hospitalization episode in pediatric Oncology center at Hacettepe University between 1996 to 1999 and showed the reasons as diagnostic procedures 8.0%, chemotherapy 57.5%, biopsy/operation, 22.1%, infections/neutropenic fever 10.4%, follow-up 1.4%, metabolic disturbances 0.3%, and others 0.3% for 682 children with lymphoma and solid tumors. The leading tumors which requires hospitalization were lymphomas 36.0%, soft tissue sarcomas 11.3%, neuroblastoma 9.7%, bone tumors 8.8%, CNS tumors 5.8%, renal tumors 5.8%. About 70.3% were hospitalized in the pediatric wards (ICU 2.4%, infectious disease 7%, adolescence 24.0%, school age 25.6%, preschool 4.1%, infancy 7.0%, newborn 0.2%) and 29.7% were in surgical and nonpediatric wards (pediatric surgery 12.4%, neurosurgery 7.1%, orthopedics 4.1%, ophthalmology 2.9%, internal medicine 0.9%, other surgical 2.3%). The median days spent in the hospital were 8 days for pediatric wards and 11 days for surgical and nonpediatric wards and 9 days for the whole group.

We also analyzed the hospital resource utilization data for 223 children with all types of malignant tumors diagnosed in 2004. The follow-up period for the analysis of these data were the years of 2004 to 2006. The male/female ratio was 1.23 (123/100). The mean age for the study group was 6.92 ± 4.96 (range 0 to 17). The distribution of tumor types in 223 children were leukemia 11.65%, lymphoma/RES13.45%, CNS/intracranial/intraspinal 29.14%, sympathetic tumors 1.79%, RBL 6.72%, renal tumors 6.72%, liver tumors 4.84%, malign bone tumors 4.03%, STS 6.27%, germ cell/trophoblastic/gonadal 3.58%, carcinoma/other epithelial 10.31%, other unspecified 1.34%, unknown 0.44%. Outpatient and inpatient distribution of the hospital visits were evaluated for the follow-up period. The outpatient visit numbers were 2545 visits (range 1 to 62 times) for 220 patients (3 patients were seen as inpatient only). Total costs for 2545 outpatient visits were 860948.85 USD with a mean cost of 3895.69 USD (minimum cost 1.49 USD and maximum cost 430474.42 USD). There were 439 admissions (1 to 17 times, mean 2.81) for 156 patients. Total days spent in the hospital were 2189 (0 to 92 d). The total costs for 439 admissions were 1567065.75 USD with a mean cost of 10660.31 USD (range 42.28 to 247729.63 USD). Table 1 showed the distribution of the costs for the different types of services in childhood tumors with a total cost of 2058148.97 USD. As a summary, the outpatient cost was 860948.85 USD, inpatient cost 1567065.75 USD, other services 2058148.97 USD and total costs were 223 children for 3 years follow-up was 4486163.57 USD. Three-year overall survival for whole group was found as 76.5%.

TABLE 1. Three-year Costs for Different Services in 223 Children With Malignant Tumors

Type of the Service	Total Number	Total Costs (USD)
Operation	628	1134448.32
CT	740	43354.03
MRI	268	20084.61
Nuclear imaging	218	14844.06
Other radiologic investigation	2452	49222.11
Drugs	8554	620252.85
Blood products	321	63713.69
Chemotherapy	584	43552.26
Consultations	948	9576.36
Laboratory	40466	487602.33
Examinations	2153	22305.86
Pathology	463	24929.53
Radiotherapy	505	95796.81
Others	5528	211565.38
Medical supplies	6122	141988.18
Beds	896	95912.60
Total		2058148.97

Pediatric Tumor Registry for 2002-2005 in Turkey

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In a previous study from a major pediatric oncology center in Turkey, the data shows the tumor distribution (solid tumors and lymphomas only) as followed: lymphoma 34.7%, CNS tumors 4.0%, soft tissue sarcomas 9.7%, renal tumors 9.5%, sympathetic system 9.4%, germ cell 6.7%, bone tumors 6.0%, carcinoma and other epithelial 3.9%, retinoblastoma 2.6%, liver tumors 1.6%, rare tumors 0.6%, unclassified 1.2% among 5859 children diagnosed and followed-up during 1971 to 2000. We also have observed a significant improvement in survival rates from early 70s through late 90s in this group. Following this analysis, we established a hospital-based cancer registry in Hacettepe University in 2002 and were able to register 223 cases for the year of 2004. However, the nationwide data on pediatric cancers are limited in Turkey. The only reliable data comes from Cancer Registry from Izmir Region.

Lack of cancer registry and inadequate data collection became a challenge for us to establish a nationwide pediatric cancer registry in Turkey. In 2002, Turkish Pediatric Oncology Group started to collect registry data of 1073 childhood cancer from 33 pediatric oncology centers (Table 1). Leukemias were not included in this analysis. Two-year survival rates for this group was 66.3%.

Turkish Pediatric Oncology Group and Turkish Pediatric Hematology Association made a collaboration to establish a more comprehensive pediatric cancer registry in 2005. A Web-based tool for data entry for first nationwide data collection was established and we are getting data from > 60 participating centers since 2005. The preliminary data shows the distribution of the tumors in 1435 childhood tumors as: leukemia 27.2%, lymphomas and RES 16.7%, CNS/intracranial/intraspinal 11.6%, sympathetic system 10.6%, retinoblastoma 2.8%, renal tumors

5.4%, hepatic tumors 0.9%, malignant bone tumors 5.2%, soft-tissue sarcomas 7.7%, germ cell/trophoblastic/other gonadal 4.7%, carcinomas/other malignant epithelial 4.7%, other/unspecified malignant) 2.0%, LCC 0.5%.

We believe that the collaboration of 2 major pediatric groups will be able to create a major source on pediatric cancers in Turkey and this will be useful for planning research and services in pediatric oncology in our country.

TABLE 1. Tumor Types in 1073 Children With Lymphoma and Solid Tumors, 2002 (Turkish Pediatric Oncology Group, TPOG Pediatric Tumor Registry)

Tumor Type	Male/Female	Number	%
Lymphoma	195/92	287	26.80
NHL	124/57	181	16.90
Hodgkin	71/35	106	9.90
M. histiocytosis	1/0	1	0.10
CNS tumors	134/93	227	21.10
Sympathetic system tumors	49/52	101	9.40
Soft tissue tumors	46/35	81	7.50
Renal tumors	35/41	76	7.10
Osteosarcoma	37/23	60	5.60
Ewing tumor	27/18	45	4.20
Chondrosarcoma	1/0	1	0.10
Retinoblastoma	18/31	49	4.60
Germ cell tumors	34/31	65	6.10
Liver tumors	18/5	23	2.10
Carcinoma/others	29/28	57	5.30
Total	624/449	1073	100.00

Psychosocial Aspects of Pediatric Palliative Care

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"*We are in need of medicine with a heart….*"

Salvador Avila, parent, 2001[1]

Children need to understand what is happening to them. When diagnosed with a life-threatening illness, they come to terms with the multiple medical demands, physical and social changes, as well as psychologic challenges through psychotherapy and ongoing conversations with trusted health care professionals.[1–3] Dealing with trauma can be addressed over successive psychotherapy sessions and conversations that take place at the bedside, in a playroom, or a treatment room. Child-centered, developmentally appropriate experiences, using play objects, toys, images, or metaphors, help children process what has happened so that they can make sense of this complex process and the threat to their lives.[4] Often they explore the loss of life as it used to be; restrictions on school, friends, and previous activities; the experience of feeling sick, despondent, and vulnerable; and attempts to understand and develop coping strategies to deal with painful and distressing treatments.[5,6] When given these opportunities in a safe, trusted, and therapeutic environment, children display insight and wisdom about life and its fragility.[6]

Best practice recommends addressing the psychologic needs of the child and family at diagnosis of a life-threatening disease and continues throughout the course of the child's care, whatever the outcome. The focus is on attaining the best quality of life regardless of whether the child can be cured or not.[1–3] Psychotherapy for children who are living while knowing they are dying, provides the opportunity to express profound grief and the "integration of all that he or she has lived, albeit in an abbreviated lifespan." (Ref. 5, p. 97). The therapist must be able to "enter the threat with the child, accompanying him or her down the road toward ultimate separation…The child can derive profound comfort from the safety and "ongoingness" afforded within its framework." (Ref. 5, p. 97).

The philosophy of palliative care for children living with a life-threatening illness is one that avoids the dichotomy of cure versus comfort-care.[1–3] Symptom management—the control of pain and other symptoms—is considered one cornerstone of palliative care. Another is the management of the child's psychologic, social, and spiritual concerns.[1,2] Palliative care for children requires the active total care of the child's body, mind, and spirit, and involves giving support to the parents and siblings in the family.[3]

In pediatric palliative care there is a recognition that a cohesive multidisciplinary team of pediatric health professionals is essential. The team share information among themselves and with the child and the family. The family is the unit of care and is an integral part of the treatment. The child needs to be involved, playing a part with parental support in decision-making. This process can provide a sense of healing that contributes to easing the child and family's grief and bereavement.

"*The goal is to add life to the child's days, not simply days to the child's life.*"

(Ref. 7, p. 351).

References:

1. Field M, Behrman RE, eds. *When Children Die*. Washington, DC: Institute of Medicine. The National Academies Press; 2003.
2. Carter BS, Levetown M. *Palliative Care for Infants, Children, and Adolescents*. Baltimore: The Johns Hopkins University Press; 2004.
3. Pediatric Hospice Palliative Care: Guiding Principles and Norms of Practice. Canadian Hospice Palliative Care Association and Canadian Network of Palliative care for Children. March, 2004. Available at: http://www.chpca.net/marketplace/pediatric_norms/pediatric_norms.htm#download, 2004.
4. Aasgaard T. Children expressing themselves. In: Goldman A, Hain R, Liben S, eds. *Oxford Textbook of Palliative Care for Children*. Oxford University Press; 2006.
5. Sourkes B. Psychological impact of life-limiting conditions on the child. In: Goldman A, Hain R, Liben S, eds. *Oxford Textbook of Palliative Care for Children*. Oxford University Press; 2006.
6. Kuttner L. Making every moment count. Documentary film (38 min) on pediatric palliative care. Distributed by The National Film Board of Canada 800-267-7710 or Fanlight Productions Boston 800-937-4113, 2003.
7. American Academy of Pediatrics. Palliative care for children. *Pediatrics*. 2000;106:351–357.

Cancer Survivors: Childhood and Beyond

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Combined with improvements since 1970 in surgical techniques, radiation therapy and the use of supportive therapies, clinical trials now show that 75% of children with cancer in developed countries can be cured. However, the therapy these children received often places them at risk for consequences in the future, and will continue to do so as they age. Research regarding late consequences of therapy began with case series following anecdotal reports, and evolved to include prospective studies with analysis of multiple variables. Now the emphasis is on studying the value of surveillance and intervention, particularly in populations at high risk for late effects.

The late complications of therapy for children who survive cancer can be categorized as follows:

Growth and development, including linear growth, intellectual function, and sexual maturation.

Vital organ function, especially cardiac, pulmonary, renal, and gastrointestinal.

Reproduction, including fertility and the health of offspring.
Second neoplasms, both benign and malignant; and
Psychologic health and well-being.

Research concerning late effects in survivors has resulted in the reduction or omission of radiation therapy or reducing doses in leukemia, Wilms tumor, Hodgkin disease, non-Hodgkin lymphoma, and central nervous system tumors. There is now less cardiac dysfunction because the total dose of anthracyclines has been limited and gonadal dysfunction has been reduced by avoiding radiation to the gonads and by limiting the total dose of alkylating agents to boys. Secondary leukemia has been virtually eliminated by substituting cyclophosphamide for mechlorethamine in the treatment of Hodgkin disease.

Second malignant neoplasms (SMNs) are a major late effect after childhood cancer. They develop as a result of genetic predisposition, therapy with radiation and chemotherapy, and may occur spontaneously or without a known etiology. Prominent genetic conditions in pediatrics that increase the risk for SMN include neurofibromatosis type 1 and the genetic form of retinoblastoma. Radiation increases the risk of bone and soft-tissue sarcomas, thyroid neoplasms, breast cancer, and tumors of the central nervous system. Secondary acute and chronic myeloid leukemia have been seen after therapy with alkylating agents and topoisomerase inhibitors such as epipodophyllotoxins, the latter being especially schedule dependent. The overall risk of SMN is about 6 times expected in the general population of same age individuals. The Childhood Cancer Survivor Study has now recorded 510 SMN in more than 14,000 survivors, about half occurring more than 15 years from the diagnosis of childhood cancer. All but 11% developed after radiation therapy.

Programs for childhood cancer survivors have been developed with the goals of increasing survivors' knowledge of therapy-related risk factors, and to provide surveillance and early detection of potential late effects. In addition, reproductive counseling, health education, and psychosocial support are incorporated. As childhood cancer survivors age it is critical that providers develop methods appropriate to each situation for a seamless transition to an adult health care setting. Unfortunately, qualified health care providers with knowledge of late effects are limited. For this reason a set of guidelines to be used in following survivors has been developed by the Children's Oncology Group. They may be accessed on the web at: http://www.survivorshipguidelines.org.

An Intermediary Analysis of the Neuroblastoma Treatment Protocol—2003 of the Turkish Pediatric Oncology Group (TPOG) at October 2006

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Aim: The aim of the Neuroblastoma Treatment Protocol-2003 of the Turkish Pediatric Oncology Group (TPOG) is determination of the number and characteristics of the patients with neuroblastoma; developing the most suitable treatment strategies for neuroblastoma under national conditions and standardization of the neuroblastoma treatment in Turkey.

Patients and Method: Twenty-one Pediatric Oncology centers were participated to this treatment protocol. It was activated at October 1, 2002. Of 213 patients who were assessed for the study, 195 (92%) were found to be eligible. Patients were staged according to the international neuroblastoma staging system, and the risk groups were determined according to the stage of disease, age of the patients, histopathologic examination, and MYCN amplification. The patients with high-risk disease were randomized to conventional chemotherapy or high-dose chemotherapy and autolog stem cell transplantation (HDCT-ASCT) branches at the time of diagnosis. An intermediary analysis results of 195 patients were reported here.

Results: The diagnosis was neuroblastoma in 174 (89%) and ganglioneuroblastoma in 21 (11%) patients. Male to female ratio was 1.01. The median age of diagnosis was 22 months (0.3 to 210 mo) and the number of patients under 12 months was 58 (30%). The median duration of symptoms was 1 month (0 to 18 mo). Thirty (15%) patients were diagnosed by the presence of positive radiologic findings, bone marrow involvement and high vaniylmandelic acid levels in 24-hour urine. In another 165 (85%) patients diagnosis was made by histopathologic examination. The most common primary tumor sites were adrenal gland in 115 (59%), paraspinal thoracal in 31 (16%), paraspinal abdominal-pelvic in 26 (13%) patients. At the time of diagnosis 109 (56%) patients were metastatic, and the most common sites of metastasis were bone and bone marrow in 28 (14%), bone marrow in 11 (6%) patients. The stage distribution of patients was as following: 25 (13%) in stage 1; 13 (7%) in stage 2a; 10 (5%) in stage 2b; 41 (21%) in stage 3; 94 (48%) in stage 4; and 12 (6%) in stage 4S. The MYCN analysis was performed in 107 patients, and MYCN amplification that was above 10 copies was found in 29 (27%). The risk group distribution of the patients was as following: 114 (59%) in high-risk, 56 (29%) in intermediate-risk, and 25 (12%) in low-risk groups.

In low-risk group, chemotherapy was not given to patients in stage 1; patients in stages 2a and 2b received chemotherapy including cisplatin, vincristine, and ifosfamide after surgery; patients in stage 4S received low-dose chemotherapy including cyclophosphamide and vincristine. Patients in intermediate-risk group received consecutive chemotherapy cycles including vincristin, ifosfamide, dacarbazine, adriamycine and cisplatin, cyclophosphamide, etoposide, and if the viable tumor is present after chemotherapy radiotherapy was applied. Patients in high-risk group received consecutive chemotherapy cycles including vincristin, ifosfamide, dacarbazine, adriamycine and cisplatin, cyclophosphamide, etoposide. The conditioning regimen consisting carboplatin, etoposide, melphalan was given in HDCT-ASCT group. Radiotherapy was applied to all patients for local control in high-risk group. Maintenance therapy including cyclophosphamide, vincristine, and 13-cis retinoic acid was given for patients in intermediate and high-risk groups.

The median follow-up time was 9.25 months (0.07 to 52 mo), and the 4 years event-free survival (EFS) and overall survival (OS) rates were 47% and 57%, respectively. The 4-years EFS rates were 72%, 32%, and 30% and the 4-years OS rates were 90%, 40%, and 45% in low-risk, high-risk conventional chemotherapy, and high-risk HDCT-ASCT groups, respectively. The 3-years EFS and OS were 71% in an intermediate-risk group. Relapses developed in 23 patients, and 3 of them were isolated central nervous system relapses which was out of the primary tumor. Ten (5%) patients died with chemotherapy toxicity.

Conclusions: Majority of patients had advanced stage disease (69%) and in high-risk group (59%). Therapy results were acceptable. Consequence of increasing in the number of patients, the follow-up time, and the progression-free survival, new treatment strategies may be required for central nervous system prophylaxis in some selected high-risk patients at the time of diagnosis.

An Introduction to the Pathology of Pediatric Tumors

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Renal tumors in children represent 8% of all pediatric malignancies. More than 80% of renal tumors of childhood are Wilms tumor (nephroblastoma). It is an embryonal neoplasm derived from nephrogenic blastemal cells. Tumor cells may show blastemal, epithelial and stromal differentiation. The pathologist can give information about the prognostic factors for a nephroblastoma. Prognostic factors are presence and type of anaplasia (focal or diffuse), involvement of renal sinus and the presence of nephrogenic rest.

Anaplasia is defined as the presence of multipolar mitotic figures, nuclear enlargement (3 times) and marked hyperchromatism. Tumors with anaplasia are less sensitive to chemotherapy. Focal anaplasia is the presence of a clearly defined focus within a primary intrarenal tumor, without evidence of anaplasia or nuclear atypia in extrarenal tumor sites. Nephroblastoma with focal anaplasia is an intermediate-risk tumor. Nephroblastoma with diffuse anaplasia is a high-risk tumor.

Vascular invasion in renal sinus has prognostic importance.

Nephrogenic rests: Patients with any type of nephrogenic rest in a kidney removed for Wilms tumor should be considered at increased risk for

tumor formation in the remaining kidney. The risk is greatest with intralobar rests.

Differential diagnosis of pediatric renal tumors include Wilms tumor (85%), mesoblastic nefroma (5%), clear cell sarcoma (4%), rhabdoid tumor (2%), and others (4%) (neurogenic tumors, renal cell carcinoma, angiomyolipoma, and lymphoma).

Mesoblastic nephroma is a monomorphous renal neoplasm which is usually recognized in early infancy (first 3 mo of life). It is a well-demarcated tumor but commonly extends beyond the renal capsule. Cellular pattern of the tumor has increased cellular density and pleomorphism with a high proliferative rate and a sarcomatous appearance. When a nephrogenic rest in the same kidney is seen, the remaining kidney of the patient is at risk for tumor formation.

Renal angiomyolipoma is a rare pediatric renal tumor. The average age at diagnosis is 41 years. The tumor is composed of adipose tissue, blood vessels, and smooth muscle cells. Association with tuberous sclerosis is reported. Thick-walled blood vessels, HMB 45-positive smooth muscle cells around vessels are diagnostic for this tumor.

Small round cell malignant tumors of childhood are Ewing sarcoma/primitive neuroectodermal tumor (ES/PNET), undifferentiated neuroblastoma, rhabdomyo-sarcoma, lymphoblastic lymphoma, and small cell osteosarcoma. Immunohistochemistry can help the pathologist to differentiate these tumors.

Primitive neuroectodermal tumor (PNET) was known as synonymous with peripheral neuroblastoma and extraskeletal Ewing sarcoma in the past. It is predominantly a tumor of childhood and morphologically indistinguishable from Ewing sarcoma of the skeletal system. Characteristic reciprocal chromosomal translocation t(11;22) (q24;q12) is found in PNET. It is microscopically very similar to undifferentiated neuroblastoma. Immunohistochemical features are also similar to undifferentiated neuroblastoma. Neuroendocrine markers (PGP 9.5, Chromogranin A, Neuron Specific Enolase, and Synaptophysin) are usually positive in PNET. CD 99 (MIC 2) positivity is considered as diagnostic for this tumor. But rhabdomyosarcoma, T-cell lymphoblastic lymphoma, and poorly differentiated synovial sarcoma may also show CD 99 (MIC 2) positivity. Desmin, Myo D1, and myogenin positivity may help to diagnose rhabdomyosarcoma. LCA negative, CD 99 positive T-lymphoblastic lymphomas are problem, but T-cell markers and Tdt will be helpful for the differential diagnosis.

Pediatric core needle biopsies in the evaluation of masses are found to be diagnostic in 92% of biopsies when the biopsies are examined with immunohistochemistry, cytogenetics, flow cytometry and electron microscopy [PNET/ES: 92%, non-Hodgkin lymphoma: 88%, rhabdomyosarcoma: 100%, sarcoma (NOS): 100%, Wilms tumor: 75%, germ cell tumor: 100%, neuroblastoma: 100%, ganglioneuroma: 100%].

Diagnostic problems with pediatric core needle biopsies are necrotic tumor cells, insufficient tumor cells, suboptimal immunohistochemistry due to necrosis and edge artifacts in immunohistochemistry associated with false-positive staining.

Natural History of HPV Infections and Vaccines in Prevention of Cervical Cancer

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Epidemiology: HPV is the most common sexually transmitted disease.[1] Fifty percent to 75% of these are with high-risk HPV (hrHPV) types.[2] Infection with a hrHPV is a necessary but not sufficient cause of almost all cervical cancers, the second leading cancer in women worldwide.[3] Prevalence of HPV DNA in $\geq$1000 cervical cancer tissues from 22 countries is reported to be 99.7%.[4] This is one of the strongest statistical associations in cancer epidemiology.[5]

Virus Biology and Natural History: HPV has a double-stranded circular DNA genome consisted of 8000 base-pairs enclosed in a naked icosahedral capsid. According to tissue tropism HPV are classified in cutaneous and mucosatropic subgroups. Of approximately 40 mucosatropic types, 15 are oncogenic (including 16, 18, 31, and 45) leading to virtually all cervical cancers and precursor lesions. HPV 16 is found in 60% and HPV 18 is found in 10% to 20% of squamous cervical cancers.[6] Rate of association is also similar for adenocarcinoma: HPV 16 and 18 account for 91% of cases.[7]

When integrity of cervical epithelium is disturbed, HPV infect basal cells. Infected cells are not lysed and antigenic viral capsid proteins are not synthesized until these cells migrate up and differentiate into superficial epithelial layer,[8] therefore, immune system activation is delayed.

HPV genome has 3 functional regions: early, late, and long control regions. E5 stimulates cell growth by activating EGF receptor and inhibit p21 expression. E6 interacts with many cellular factors leading to p53 degradation, blockage of apoptosis, and intervening intercellular signaling. E7 protein inhibits Rb functions and disturbs keratinocyte differentiation. Inhibition of tumor suppressor mechanisms by these oncoproteins lead to impaired repair, therefore, accumulation of mutations. E6 and E7, major oncoproteins, constitute ideal targets for development of therapeutic vaccines.

L1 and L2, major and minor capsid proteins, enable entrance of viral DNA into host cell and constitute ideal targets for prophylactic vaccines.

Persistance: Fortunately most HPV infections subside spontaneously. If they clear completely or remain latent in basal epithelial cells is still obscure.[5] Reinfection with same type and coinfection with multiple types are possible. Acquisition and persistence of infection depends on viral, environmental, and host factors. hrHPV types[9] and larger viral load[10] are proposed risk factors for persistence. hrHPV persistence is reported to increase with age: 20% under 20 and 50% after 55 years of age.[11] Oral contraceptive use, smoking, race, dietary habbits, number of sexual partners, and age of first intercourse are also mentioned among possible risk factors.

Vaccines: There are 2 prophylactic vaccines with phase 2 trials completed. Cervarix[12,13] is a bivalent vaccine containing virus like particles (VLP) of HPV 16 and 18. Gardasil[14] is quadrivalent with VLP of HPV 6 and 11, which cause 90% of genital warts, in addition to HPV 16 and 18. VLP containing L1 proteins are noninfectious and nononcogenic as they do not include DNA, but are immunogenic and trigger production of HPV neutralizing antibodies. Antibody titers increase $\geq$50-fold higher than produced in natural infection and drop to nearly 10-fold in first 2 years and reach a plateau by third year, however, remain still above the levels induced by natural infections.[15]

Both vaccines seem equally and highly safe, immunogenic, and efficacious. Cervarix and Gardasil have 100% efficacy in preventing CIN II/III and 96% and 90% efficacy, respectively, in preventing persistent infections.

There are many questions to be answered regarding time and population of vaccination. There is no age group away from hrHPV risks: prevalence of hrHPV is 3% to 10% under 11 years. Two percent of SIL cases are diagnosed in 10 to 14-year old girls.[11] Duration of vaccine protection and need for boosting are also unknown. ACIP recommended routine vaccination of 11 to 12-year old girls. The Society of Gynecologic Oncologists offered vaccination to women 9 to 26 years old with equivocal or abnormal Pap tests, genital warts, hrHPV positivity, and immune compromise.

Antibodies extensively transudate into mucus but as lesions in men are mostly not mucosal, effectiveness in men is questionable. Furthermore, if women are highly covered by a vaccine program, vaccination of men adds little.[15]

As noncervical HPV-associated cancers are very rare, larger-scaled studies with longer follow-up are needed to assess the effectiveness of vaccines in these diseases.

There is no available data on therapeutic efficacy.

Screening practices should continue for vaccinated population.

References:

1. De Schryver A, Meheus A. Epidemiology of sexually transmitted diseases: the global picture. *Bull World Health Organ.* 1990;68:639–654.
2. Cates W Jr. Estimates of the incidence and prevalence of sexually transmitted diseases in the United States. American Social Health Association Panel. *Sex Transm Dis.* 1999;26(suppl):S2–S7.
3. Ferlay J, Bray F, Pisani P, et al. ***GLOBOCAN 2002****: Cancer Incidence, Mortality and Prevalence Worldwide. IARC Cancer Base No. 5, Version 2.0.* Lyon: IARC Press; 2004-2005.
4. Walboomers JM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol.* 1999;189:12–19.
5. Trottier H, Franco EL. The epidemiology of genital human papillomavirus infection vaccine. 2006;24S1:S1/4–S1/15.

6. Munoz N, Bosch FX, De Sanjose S, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N Engl J Med*. 2003;348:518–527.
7. Castellsague X, Diaz M, de Sanjose S, et al. Worldwide human papillomavirus etiology of cervical adenocarcinoma and its cofactors: implications for screening and prevention. *J Natl Cancer Inst*. 2006; 98:303–315.
8. Scheurer ME, Tortolero-Luna G, Adler-Storthz K. Human papillomavirus infection: biology, epidemiology, and prevention. *Int J Gynecol Cancer*. 2005;15:727–746.
9. Schlecht NF, Platt RW, Duarte-Franco E, et al. Human papillomavirus infection and time to progression and regression of cervical intraepithelial neoplasia. *J Natl Cancer Inst*. 2003;95:1336–1343.
10. Dalstein V, Riethmuller D, Pretet JL, et al. Persistence and load of high-risk HPV are predictors for development of high-grade cervical lesions: a longitudinal French cohort study. *Int J Cancer*. 2003; 106:396–403.
11. Bosch X, Harper D. Prevention strategies of cervical cancer in the HPV vaccine era. *Gynecol Oncol*. 2006;103:21–24.
12. Harper DM, Franco EL, Wheeler C, et al. Efficacy of a bivalent L1virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. *Lancet*. 2004;364:1757–1765.
13. Harper DM, Franco EL, Wheeler C, et al. Sustained efficacy up to 4.5 years of a bivalent L1virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial. *Lancet*. 2006;367:1247–1255.
14. Villa LL, Costa RL, Petta CA, et al. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. *Lancet Oncol*. 2005; 6:271–278.
15. Schiller JT, Lowy DR. Prospects for cervical cancer prevention by human papillomavirus vaccination. *Cancer Res*. 2006;66:10229–10232.

Potential Therapeutic Targets in Liver Cancer

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Cancer is a disease of cells having the capacity for uncontrolled growth and tissue invasion, due to genetic and epigenetic changes. Today, specific changes that occur in many different cancer types are known, as result of intense research activities in molecular biology and genetics. Changes that are known in cancer cells can be grouped into 5 main groups: (1) self sufficiency for proliferation; (2) insensitivity to growth inhibitory signals; (3) resistance to apoptosis or programmed cell death; (4) immortality or limitless proliferation potential; (5) ability for tissue invasion and metastasis. Molecular details of the first 4 characteristics just stated are well known. Cancer cell acquire these features as a result of aberrant function of genes that are broadly classified as ''oncogenes'' and ''tumor suppressor genes.'' Oncogenes usually allow cancer cells to proliferate, to resist to apoptosis, and to gain immortality. On the other hand, tumor suppressor genes are those that inhibit such cellular processes in normal cells, but fail to do so in cancer cells due to mutations or other problems. Proteins that are encoded by oncogenes and tumor suppressor genes play key roles in pathways that regulate different cellular processes that have just been mentioned. These pathways are usually initiated by an extracellular signal that activates a cellular receptor. Then, receptors allow the amplification of the signal in the cytoplasm by enzymatic activity or protein-protein interactions. Cell nucleus is the terminal place that the signaling reaches and results in up-regulation and/or down-regulation of a set of genes. Consequently, cell will respond to an external stimulus by a change in its comportment. In cancer cells, due to mutations or epigenetic changes, aberrations occur in different signaling pathways. Signals that stimulate cell proliferation and survival are amplified, whereas the antagonistic signals are blocked. During recent years, screening of molecules that interfere with cancer signaling pathways has led to the discovery of many drug candidates. Drug candidates that act externally are usually monoclonal antibodies or recombinant proteins, whereas those acting in cancer cells are small chemicals either natural or obtained synthetically. Both approaches have been proven to be effective by the development of new drugs that are now widely used in as cancer therapeutics.

Replicative immortality is a common acquired feature of cancer. Cancer cell immortality contrasts with the intrinsic control of the number of cell divisions in human somatic cells by a mechanism called replicative senescence. Replicative immortality is acquired by inactivation of p53 and $p16^{INK4a}$ genes and reactivation of telomerase reverse transcriptase gene expression. As the inactivation of p53 and $p16^{INK4a}$ genes is often an irreversible event, it is assumed that cancer cell immortality is also irreversible. However, we recently obtained replicative senescent clones derived from a immortal hepatocellular carcinoma cell line. We showed that the reversal of immortality in these clones is accompanied by the repression of telomerase expression, and progressive telomere shortening. Replicative senescence in these clones was independent of p53 and $p16^{INK4a}$ because these clones were p53 and $p16^{INK4a}$-deficient. Additionally, we experimentally showed that the SIP1 gene encoding a transcriptional repressor protein was partly responsible for replicative senescence (Ozturk M et al, Proc Natl Acad Sci U S A, 2006:103:2178–2183). To analyze the transcriptional regulatory networks involved in senescence and the reversal of immortality, we subjected our immortal, early and late mortal (senescent) clones to microarray analysis. About 5000 genes were identified as differentially expressed in 2 sets of immortal and mortal clones. Differentially expressed genes between immortal and early mortal clones were used to extract the regulatory networks involved in the reversal of immortality and the initiation of replicative senescence program. On the other hand, differentially expressed genes between early and late mortal clones were used to extract the regulatory networks functioning in the execution of senescence program. Our preliminary analysis has revealed several signaling pathways involved in the reversal of immortality, initiation and execution of senescence program, and in cirrhosis. We expect that further genetic and functional analysis of our selected genes will identify the regulatory networks and potential target genes for the therapy of liver cancers.

Treatment of Pediatric Nasopharyngeal Cancer

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Pediatric nasopharyngeal carcinoma (NPC) constitutes 1% to 5% of all pediatric cancers and 20% to 50% of all primary nasopharyngeal malignant tumors in children.[1,2] NPC is an endemic disease of Southeast Asian countries, where the incidence rates varies from 30 to 50 in 100,000 people and it is strongly associated with Chinese ethnic origin.[1] One remarkable difference between Mediterranean and Asian (endemic) NPC's is age distribution. Although a unimodal peak at the fifth or sixth decade exist in endemic countries, a second minor early peak at 10 to 20 years of age exists at Mediterranean region countries. The rate of pediatric patients account 6% to 18% of all NPC patients in these countries, same figure is reported to be $< 1\%$ of all NPC's in endemic countries.[2–14]

Although the concomitant chemotherapy and radiation, with or without adjuvant chemotherapy, is now the standard care for adult patients, neoadjuvant chemotherapy with radiotherapy has gained popularity parallel to other pediatric treatment protocols in various solid tumors.[1,2,18] Radiotherapy has been the mainstay of the treatment both in adults and pediatric NPC patients.[1,2] However, due to the rarity of pediatric NPC, most published series are quite heterogeneous in terms of patient, tumor, and treatment characteristics.[2,9,11,12,17–20,24] The pediatric NPC literature can be classified in 3 groups: older retrospective series, more recent retrospective series, and prospective series. The first group's manuscripts typically included few patients, with inadequate locoregional and distant staging, and with suboptimal treatment modalities.[3,17,18,25–29] Results of these manuscripts generally proposed the use of total tumor doses in the range of 35 to 86 Gy and point out the need for effective systemic treatment in addition to radiotherapy. The second group of manuscripts were published in 1990s, with better local and systemic staging of the disease and improved treatment parameters.[4,5,7–10,12,13,16,19,21–23,30–33] The majority of these retrospective studies found the optimum dose to the primary tumor to be between 50 and 70 Gy, with the suggestion of higher efficacy with doses greater than 60 to 66 Gy in some reports.[7,10,15,20,24,31] Superior results were reported with use of cisplatin-based chemotherapy and neoadjuvant

chemotherapy compared with regimens without cisplatin and adjuvant chemotherapy schedules.[7,9,16] There are only 2 reported prospective studies in the literature and these comprise the third group.[34–36] A prospective German trial, conducted in the early 1990s, treated patients with 3 courses of neoadjuvant chemotherapy with adjuvant recombinant IFN-β for 6 months.[35] A total dose of 59.4 Gy was given for all patients, independent of T status, with a response rate of 91%. In their study, 58 of 59 patients responded to chemotherapy and only 1 patient progressed during chemotherapy. The second study was reported recently by the Pediatric Oncology Group.[36] Stages III to IV patients were treated with 4 courses of preradiation chemotherapy. The primary tumor and involved lymphatics were treated to a total tumor dose of 61.2 Gy with a shrinking field technique. The overall response rate to induction chemotherapy was 93.7% with 4-year event-free and overall survival rates of 77% and 75%, respectively. The investigators initiated the new ARAR 0331 study where they will explore the use of induction chemotherapy followed by concurrent chemotherapy. Both studies revealed that dose reduction to 60 Gy is feasible. However, the overall and disease-free survival rates were superior in the German study compared with US study, despite the fact that the POG study patients received 1 chemotherapy cycle more and a slightly higher total radiotherapy dose. The superior results of German series may be explained by the application of adjuvant immunologic treatment or the different biology of the disease in 2 countries.

Recently, retrospective analysis of 74 pediatric NPC patients at the Gustave Rousy Institute (IGR) was reported in 2004.[37] Either low-dose radiotherapy (50 Gy) was administered to good responders to neo-adjuvant chemotherapy (54% of patients) or high-dose radiotherapy (65 to 70 Gy). Despite a similar locoregional recurrence rate for the 2 groups, event-free and overall survival rates were better in the low-dose radiotherapy group. Authors concluded that response adapted dose reduction seems to be possible in selected pediatric NPC patients.

At this time, the standard treatment of pediatric NPC consists of high-dose radiotherapy and chemotherapy.[2] However, radiotherapy treatment can be associated with severe long-term toxicities. The pediatric NPC is one of the pediatric malignancy where significant radiotherapy dose reduction have not yet been proven, although the results of the 2 prospective studies and retrospective IGR analysis suggest this may be possible. Therefore, every effort should be made to prevent these patients from severe late sequela without jeopardising the good disease control. However, research should be encouraged in an attempt to reduce the potential for long-term sequelae in pediatric patients given their relatively favorable prognosis and potential for longevity.

References:

1. Wei W, Sham JST. Nasopharyngeal carcinoma. *Lancet*. 2005;365: 2041–2054.
2. Ayan I, Kaytan E, Ayan N. Childhood nasopharyngeal carcinoma: from biology to treatment. *Lancet Oncol*. 2003;4:13–21.
3. Cammoun M, Hoerner V, Mourali N. Tumors of the nasopharynx in Tunisia. An anatomic and clinical study based on 143 cases. *Cancer*. 1974;33:184–192.
4. Daoud J, Toumi N, Bouaziz M, et al. Nasopharyngeal carcinoma in childhood and adolescence: analysis of a series of 32 patients treated with combined chemotherapy and radiotherapy. *Eur J Cancer*. 2003;39:2349–2354.
5. Sahraoui S, Acharki A, Benider A, et al. Nasopharyngeal carcinoma in children under 15 years of age: a retrospective review of 65 patients. *Ann Oncol*. 1999;10:1499–1502.
6. Schmauz R, Templeton AC. Nasopharyngeal carcinoma in Uganda. *Cancer*. 1972;29:610–621.
7. Ayan I, Altun M. Nasopharyngeal carcinoma in children: retrospective review of 50 patients. *Int J Radiat Oncol Biol Phys*. 1996;35:485–492.
8. Uzel O, Yoruk SO, Sahinler I, et al. Nasopharyngeal carcinoma in childhood: long-term results of 32 patients. *Radiother Oncol*. 2001;58:137–141.
9. Kupeli S, Varan A, Ozyar E, et al. Treatment results of 84 patients with nasopharyngeal carcinoma in childhood. *Pediatr Blood Cancer*. 2005.
10. Selek U, Ozyar E, Ozyigit G, et al. Treatment results of 59 young patients with nasopharyngeal carcinoma. *Int J Pediatr Otorhinolaryngol*. 2005;69:201–207.
11. Berberoglu S, Ilhan I, Cetindag F, et al. Nasopharyngeal carcinoma in Turkish children: review of 33 cases. *Pediatr Hematol Oncol*. 2001;18:309–315.
12. Serin M, Erkal H, Elhan AH, et al. Nasopharyngeal carcinoma in childhood and adolescence. *Med Pediatr Oncol*. 1998;31:498–505.
13. Har-Kedar I, Chaitchik S, Hercberg A. Nasopharyngeal carcinoma at the Tel-Hashomer Government Hospital, Israel. A 20 year survey (1951-1970). *Clin Radiol*. 1974;25:403–407.
14. Huang TB. Cancer of the nasopharynx in childhood. *Cancer*. 1990;66:968–971.
15. Khabir A, Ghorbel A, Daoud J, et al. Similar BCL-X but different BCL-2 levels in the two age groups of north African nasopharyngeal carcinomas. *Cancer Detect Prevent*. 2003;27:250–255.
16. Fernandez CH, Cangir A, Samaan NA, et al. Nasopharyngeal carcinoma in children. *Cancer*. 1976;37:2787–2791.
17. Al-Sarraf M, LeBlanc M, Giri PG, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. *J Clin Oncol*. 1998;16:1310–1317.
18. Deutsch M, Mercado R Jr, Parsons JA. Cancer of the nasopharynx in children. *Cancer*. 1978;41:1128–1133.
19. Pao WJ, Hustu HO, Douglass EC, et al. Pediatric nasopharyngeal carcinoma: long term follow-up of 29 patients. *Int J Radiat Oncol Biol Phys*. 1989;17:299–305.
20. Ingersoll L, Woo SY, Donaldson S, et al. Nasopharyngeal carcinoma in the young: a combined M.D. Anderson and Stanford experience. *Int J Radiat Oncol Biol Phys*. 1990;19:881–887.
21. Ghim TT, Briones M, Mason P, et al. Effective adjuvant chemotherapy for advanced nasopharyngeal carcinoma in children: a final update of a long-term prospective study in a single institution. *J Pediatr Hematol Oncol*. 1998;20:131–135.
22. Wolden SL, Steinherz PG, Kraus DH, et al. Improved long-term survival with combined modality therapy for pediatric nasopharynx cancer. *Int J Radiat Oncol Biol Phys*. 2000;46:859–864.
23. Zubizarreta PA, D'Antonio G, Raslawski E, et al. Nasopharyngeal carcinoma in childhood and adolescence: a single-institution experience with combined therapy. *Cancer*. 2000;89:690–695.
24. Martin WD, Shah KJ. Carcinoma of the nasopharynx in young patients. *Int J Radiat Oncol Biol Phys*. 1994;28:991–999.
25. Jereb B, Huvos AG, Steinherz P, et al. Nasopharyngeal carcinoma in children review of 16 cases. *Int J Radiat Oncol Biol Phys*. 1980;6: 487–491.
26. Berry MP, Smith CR, Brown TC, et al. Nasopharyngeal carcinoma in the young. *Int J Radiat Oncol Biol Phys*. 1980;6:415–421.
27. Jenkin RD, Anderson JR, Jereb B, et al. Nasopharyngeal carcinoma—a retrospective review of patients less than thirty years of age: a report of Children's Cancer Study Group. *Cancer*. 1981;47:360–366.
28. Lombardi F, Gasparini M, Gianni C, et al. Nasopharyngeal carcinoma in childhood. *Med Pediatr Oncol*. 1982;10:243–250.
29. Gasparini M, Lombardi F, Rottoli L, et al. Combined radiotherapy and chemotherapy in stage T3 and T4 nasopharyngeal carcinoma in children. *J Clin Oncol*. 1988;6:491–494.
30. Sham JS, Poon YF, Wei WI, et al. Nasopharyngeal carcinoma in young patients. *Cancer*. 1990;65:2606–2610.
31. Laskar S, Sanghavi V, Muckaden MA, et al. Nasopharyngeal carcinoma in children: ten years' experience at the Tata Memorial Hospital, Mumbai. *Int J Radiat Oncol Biol Phys*. 2004;58:189–195.
32. Nakamura RA, Novaes PE, Antoneli CB, et al. High dose-rate brachytherapy as part of a multidisciplinary treatment of nasopharyngeal lymphoepithelioma in childhood. *Cancer*. 2005;104:525–531.
33. Polychronopoulou S, Kostaridou S, Panagiotou JP, et al. Nasopharyngeal carcinoma in childhood and adolescence: a single institution's experience with treatment modalities during the last 15 years. *Pediatr Hematol Oncol*. 2004;21:393–402.
34. Mertens R, Granzen B, Lassay L, et al. Nasopharyngeal carcinoma in childhood and adolescence: concept and preliminary results of the cooperative GPOH study NPC-91. Gesellschaft fur Padiatrische Onkologie und Hamatologie. *Cancer*. 1997;80:951–959.

35. Mertens R, Granzen B, Lassay L, et al. Treatment of nasopharyngeal carcinoma in children and adolescence: Definitive results of a multicenter study (NPC-91-GPOH). *Cancer*. 2005;104:1083–1089.
36. Rodriguez-Galindo C, Wofford M, Castleberry RP, et al. Preradiation chemotherapy with methotrexate, cisplatin, 5-Fluorouracil, and Leucovorin for pediatric nasopharyngeal carcinoma. Results of Pediatric Oncology Group (Now Children's Oncology Group) Study 9486. *Cancer*. 2005;103:850–857.
37. Habrand J, Valls DG, Petras S, et al. Carcinoma of the nasopharynx in children and adolescents treated with initial chemotherapy followed by adapted doses of radiotherapy. Proceedings of 46th Annual ASTRO Meeting. *Int J Radiat Oncol Biol Phys*. 2004;S247:191.

The Middle East Cancer Consortium—MECC

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The organizational aim of MECC is to decrease the burden of cancer in this region, through collaboration between its members—Egypt, Cyprus, Israel, Jordan, The Palestinian Authority, Turkey, and the United States.

Our journey through life starts at birth. Infancy is followed by childhood, adulthood, raising a family, reaching a golden age, and ends at our death. In recent years, cancer has become a very dominant disease in our societies. This can be attributed to ageing, stress, increased smoking, obesity, decreased physical activity, etc. This disease affects all age groups, but especially the elderly.

The MECC story started in the mid-1990s in Washington, DC, when President Clinton's mother was at a terminal stage of cancer. Among her last requests was the wish that something be done about this horrible disease. At the same time the Clinton administration had initiated settlement talks between the Israelis and the Palestinians. This noteworthy occurrence prompted the President to approach his Secretary of Health and Human Services, Donna Shalala, and Secretary of State, Madeline Albright, with a request to try to proactively respond to these initiatives.

Consultations with the directors of the National Institutes of Health and the National Cancer Institute resulted in an agreement to establish the MECC, which was signed on May 20, 1996, in Geneva, Switzerland. The founding ministers who signed the agreement, in the presence of Secretary Donna Shalala, from the United States were:

Minister Ismail Salam, from Egypt
Minister Ephraim Sneh, from Israel
Minister Manolis Christofides, from Cyprus
Minister Ma'arouf Bataynea, from Jordan
Deputy Minister Munzer Sherif, from The Palestinian Authority.

MECC focuses its activities among the 6 members that comprise the consortium: Egypt, Jordan, Cyprus, The Palestinian Authority, Turkey, and Israel. The highest body governing the MECC is the Ministerial Committee whose members are the Ministers of Health of each member state. This committee approves the annual report, including the financial report, presented by the Board of Governors, and has the sole authority to accept new members into the MECC.

Day-by-day operations are based on decisions made by the Board of Governors. Each member of the board is nominated by his/her respective Minister of Health. The Board of Governors recommends new programs and establishes the budgets for the regional activities, training programs, and for the initiation of new programs.

MECC is represented in each of its member states by a Principal Investigator (PI). The PI is responsible for his/her country's share in the ongoing regional projects such as the Cancer Registry and the Palliative Care programs. Each PI is in charge of his own staff running the current projects.

In addition, MECC, via the NCI, supports short-term fellowships for individuals from MECC countries for training in hospitals or other institutions in the region or in the United States.

The consortium started its activities with 6 members, whose representatives signed the founding agreement. Today MECC's activities have expanded to include countries further away from the Middle East, extending from Central Asia to the Maghreb, to Europe and Canada.

The people of the MECC countries speak 4 different languages, practice 3 religions, and have a variety of cultural backgrounds. Yet, our aim is to encourage people to work together in collaborative efforts, while maintaining a low profile.

The flagship project of the MECC, from the onset, has been the Regional Cancer Registry Project. Cancer Registry is the process of collecting national data about all new cancer cases each year. These data are analyzed and provide the respective Ministers of Health with accurate information on the number of cancer patients in their country. Data for the Registry is recorded using a standardized method that enables us to compare the findings among the partners. The importance of having a reliable Cancer Registry system is to enable a screening program that permits the detection of the disease at an early stage.

Within the framework of this project MECC focuses on:

- Training of registrars
- Developing manuals of standards for Cancer Registries
- Development of computer programs for standardization of the registries
- Publication of comparison studies
- Exchange fellowships
- Training in Epidemiology and Bio-sciences
- Quality control site visits and
- Support of individual researchers in MECC countries

All of these activities have been made possible thanks to the support of many agencies:

Recently, we have initiated our second regional project—Palliative Care—which is the care given to patients when all other curative treatments are no longer effective. The goal of palliative care is to relieve the patient's suffering through eliminating pain and by assisting the patient further by alleviating his sense of isolation and supporting his quality of life and self-dignity until death.

Overall, the Palliative Care project involves 3 age groups:

1. Children—we work to improve communication between sick children and their treating teams.
2. Adults—we wish to alleviate the side effects of the treatment, provide psychologic support and to assist family members to cope with their bereavement.
3. The Elderly—in this age group the main objective is to keep the patient free of pain and, concomitantly, maintain their self dignity till the very end.

On this occasion of MECC's 10th anniversary, it is satisfying to look back on what has been accomplished. To the individuals who have contributed to the MECC over the past decade, I would like to say Thank You. To those who have not yet had the opportunity to contribute, I note that our future still faces many important challenges. As we close our first decade of activities we are encountering the challenges of the future. Let us pray that God will bless us with the wisdom to cope with our future missions. That is our Hope.

The ACCIS (Automated Childhood Cancer Information System) Study

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ACCIS is a collaborative project of 80 population-based cancer registries in 35 European countries with substantial population coverage. High-quality information on 90,000 cases incident between 1978 and 1997 developed among 789 million person-years was included in various descriptive analyses of incidence and survival. Countries were grouped into 5 geographical regions: British Isles, East, North, South, and West.

Overall age-standardized incidence rate (ASR) of cancer in childhood was 139 per million in 1988 to 1997, based on 53,717 cancer cases. ASRs ranged from 131 per million in British Isles to 160 per million in the North. Geographical differences in childhood cancer incidence were found between European regions for almost all diagnostic groups. European ASR per million person-years was estimated at 44 for leukemia, 15 (lymphomas), 30 (CNS tumors), 11 (neuroblastoma), 4 (retinoblastoma), 8 (Wilms tumor), 1 (hepatoblastoma), 3 (osteosarcoma), 2 (Ewing

sarcoma of bone), 9 (soft tissue sarcomas), 5 (germ cell tumors), and 4 (epithelial tumors and melanoma).

Incidence rates increased in Europe between 1978 and 1997 by 1.1% per year (N = 77,111). The average annual change (AAC) was significant for leukemias (AAC = +0.6%), lymphomas (+0.9%), CNS tumors (+1.7%), neuroblastoma (+1.5%), renal tumors (+0.8%), soft-tissue sarcomas (+1.8%), germ cell tumors (+1.6%), and carcinomas (+1.3%). No temporal trend was seen for retinoblastoma, hepatic tumors, bone tumors, and other/unspecified tumors. The overall incidence was increasing in all 5 regions, but for none of the main tumor groups was it increasing simultaneously in all 5 geographical regions. This observation emphasises the need for large databases to evaluate the geographical and temporal evolution of childhood cancer in populations.

The reported geographical differences and changing time trends may partly reflect diversity in diagnostic and registration practices of childhood cancer in the contributing registration areas and their evolution over time. However, the nature and extent of this variability suggest also a role of underlying risk factors. Changes in genetic factors cannot be excluded, taking into account the improved medical care, which may result in affected individuals reaching the reproductive age and possibly transferring predisposition to certain cancers. The manifest decline in infant mortality might increase the susceptibility to cancer in childhood population. Important risk factors may include the increasing mobility of humans and certain changes in lifestyle and reproduction (eg, smaller families), which might cause changes in immunologic stimulation and consequently altered resistance for the presumable virus agent associated with leukemia and some other hematopoietic malignancies in children or increasing childbearing age. The exposure to a variety of artificial and natural agents has been changing over the study period and several such factors have been linked to increased risk, although the evidence is inconclusive.

TABLE 1. Five-year Survival of Children Aged 0-14 y Diagnosed With Cancer in the Periods Shown and Resident in the 5 European Regions

	Period of Diagnosis	N	5-year Survival	95% Confidence Interval
Europe	1978-82	13,800	54.4	(53.6,55.3)
	1983-87	20,718	65.2	(64.5,65.8)
	1988-92	20,880	71.2	(70.5,71.8)
	1993-97	20,174	75.0	(74.3,75.7)
British Isles	1978-82	6042	54.3	(53.0,55.5)
	1983-87	6083	63.8	(62.5,65.0)
	1988-92	6526	69.4	(68.3,70.5)
	1993-97	4485	74.2	(72.8,75.4)
East	1978-82	1963	46.1	(43.9,48.3)
	1983-87	2220	52.4	(50.2,54.5)
	1988-92	2242	58.3	(56.2,60.4)
	1993-97	2141	62.7	(60.3,64.9)
North	1978-82	1941	60.0	(57.8,62.2)
	1983-87	2006	69.8	(67.7,71.7)
	1988-92	2013	76.2	(74.3,78.0)
	1993-97	2205	77.6	(75.6,79.5)
South	1978-82	1136	53.2	(50.2,56.1)
	1983-87	1363	63.0	(60.3,65.5)
	1988-92	1264	69.6	(67.0,72.1)
	1993-97	1186	74.4	(71.5,77.0)
West	1978-82	360	54.4	(49.1,59.5)
	1983-87	6553	70.7	(69.6,71.9)
	1988-92	8175	75.1	(74.1,76.0)
	1993-97	8698	78.2	(77.1,79.2)

N indicates number of cases included in the analysis for each region. Source: ACCIS.

The ACCIS project also allows evaluating population-based survival as the ultimate measure of cancer control efforts, including targeted education for early diagnosis, timely access to care, and best available treatment protocols, accompanied by efficient supportive care. Over the period 1978 to 1997, 5-year survival has increased significantly in Europe overall and in each of the 5 regions (Table 1).

Incidence patterns and trends, and population-based survival, are described in detail in the special issue of European Journal of Cancer of September 2006 "Cancer in children and adolescents in Europe." Geographical and temporal extension of the ACCIS database is a prerequisite for continuous monitoring of childhood cancer burden in Europe.

Classification of Childhood Cancers

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Epidemiologic data for cancer have traditionally been presented according to the International Classification of Diseases (ICD), which is largely based on primary site. This is reasonably satisfactory for adults, among whom most solid cancers are carcinomas. Childhood cancers are histologically much more diverse; to classify them so that the most common types are individually specified, a scheme is needed in which much greater importance is attached to morphology. From the mid-1970s it was usual to present childhood cancer incidence data in this way, but the earliest classifications were devised for specific publications and not widely adopted.

It included all malignant neoplasms, together with nonmalignant intracranial and intraspinal tumors. There were 12 main diagnostic groups, mostly divided into subgroups. All categories were defined in terms of morphology and topography codes in the International Classification of Diseases for Oncology (ICD-O). The classification was used in the first volume of International Incidence of Childhood Cancer (IICC) and was quickly adopted as a worldwide standard.

The second edition of ICD-O featured many new morphologic entities and a new system of topography codes derived from the tenth revision of the ICD. Accordingly, a new International Classification of Childhood Cancer (ICCC) was developed, preserving as far as possible the structure of Birch and Marsden, but with the categories defined according to ICD-O-2. A few more childhood cancers of particular epidemiologic interest were given their own subgroups and, within most groups, tumours of unspecified morphology were separated from rare, specified types. ICCC was used for presentation of results in the second volume of IICC and succeeded Birch and Marsden as the standard international classification.

The advent of the third edition of ICD-O again brought a need for a new classification. It was named ICCC, third edition (ICCC-3) to indicate its relation to ICD-O-3 and to acknowledge the position of the Birch and Marsden scheme as the first truly international classification for childhood cancers.[1] It was designed to follow the rules, nomenclature, and codes of ICD-O-3, to conform to the WHO Classification of Tumors, and to accommodate new concepts while providing continuity with its predecessors. The ICD-O-3 matrix concept was followed, so that all possible neoplasms would be included so long as they had a malignant behavior code. As in previous editions, nonmalignant intracranial and intraspinal tumors were also included. The hierarchical structure was preserved, again with 12 main groups (Table 1), but certain subgroups were now further broken down into divisions in an optional "extended" classification to provide greater detail and allow aggregation of data on related entities across diagnostic groups.

The applicability of ICCC-3 to historical data and its continuity with ICCC were checked in the set of all registered childhood cancer cases that were diagnosed throughout Great Britain during 1989 to 1998 and included in the population-based National Registry of Childhood Tumors (Table 1). For most diagnostic groups the numbers were very similar in the 2 systems. Group I increased by 96 cases (2.1%) through the inclusion of myelodysplastic syndrome, not previously regarded as malignant. Group III increased by 61 cases (1.8%) with the transfer of dysembryoplastic neuroepithelial tumor from group IV and atypical teratoid/rhabdoid tumor from group IX. Within group IX there was a substantial net transfer from fibrosarcoma etc to other specified sarcomas. ICCC-3 was successfully applied to historical registry data, though allocation to divisions within group II was complicated by obsolete use of the term "lymphoblastic" for some mature B-cell lymphomas.

TABLE 1. Number of Childhood Cancers in Diagnostic Groups of ICCC-2 and ICCC-3, Great Britain, 1989-1998

	Diagnostic Group	ICCC-2	ICCC-3
I	Leukemias, myeloproliferative, and myelodysplastic diseases	4542	4638
II	Lymphomas and reticuloendothelial neoplasms	1358	1363
III	CNS and miscellaneous intracranial and intraspinal neoplasms	3375	3436
IV	Neuroblastoma and other peripheral nervous cell tumors	967	920
V	Retinoblastoma	427	427
VI	Renal tumors	801	808
VII	Hepatic tumors	122	122
VIII	Malignant bone tumors	548	548
IX	Soft tissue and other extraosseous sarcomas	1041	1022
X	Germ cell tumors, trophoblastic tumors, and neoplasms of gonads	463	460

Reference:

1. Steliarova-Foucher E, Stiller C, Lacour B, et al. International classification of childhood cancer, third edition. *Cancer*. 2005;103: 1457–1467.

Pain Management in Children With Cancer

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Children with cancer experience pain associated with the disease itself or pain caused by diagnostic and therapeutic interventions like lumbar punctures, bone marrow aspirations, surgery, or chemotherapy. Unlike adults, pain in children with cancer is predominantly treatment related. For a successful management, severity of pain must be properly assessed. Common practice is to use an observational scale like FLACC for infants, toddlers, and other children who cannot self report, to use a visual analog scale (VAS) like FACES for children who can self report and a numerical scale for children > 13-year old. Whenever possible, the cause and type of pain (nociceptive, neuropathic) should be determined and treatment of the underlying cause should be initiated.

The World Health Organization "analgesic ladder," a widely adopted management guideline, depends on a step-wise approach to pain management. It starts with nonopioid oral drugs and progresses to strong opioids, adjuvants, and invasive therapies. However, cancer pain rarely progresses in the stepwise fashion that the World Health Organization latter implies. Some new concepts have emerged like "pain emergency" that warrants rapid action. Therefore, the recent guideline of the American Pain Society recommends an "algorithm-based approach." The goal is to stay ahead of the pain, as opposed to "chasing" it.

If the child reports *mild pain*, acetaminophen (limited data for propacetamol at pediatric oncology setting) or NSAIDs (there is limited data for dosing and side effects of selective COX-2 inhibitors!) can be used initially. In case of incomplete relief, one should move to moderate pain recommendations. For patients presenting with *moderate pain*, acetaminophen or NSAIDs can be tried initially. In case they fail, codeine can be used if oral route is accessible. If not, reduced doses of strong opioids may be started. Tramadol is an effective alternative to codeine with both oral and parenteral formulations. If pain cannot be controlled with these measures, patients should be managed according to severe pain management plan.

Severe pain is an emergency and a strong opioid should be started without waiting for weaker analgesics to fail to provide relief first. It is necessary to titrate the opioid dose frequently to achieve pain relief quickly. One method is to start with a short acting opioid and instruct the family to give a dose q2h as needed for the first 24 to 48 hours. The total daily dose required to achieve pain relief is then calculated, and converted to an equivalent dose of an extended release drug or a fentanyl patch. Alternatively, morphine can be given with the physician at the bedside until the pain is controlled. Once controlled, a morphine PCA infusion may be started. If unacceptable side effects occur with morphine, hydromorphone or fentanyl can be used in equianalgesic doses. Oral administration should be used whenever possible.

Adjuvants are a heterogeneous group of drugs that can be used at any step of management either as coanalgesics (antidepressants, anticonvulsants, corticosteroids, sedative/anxiolytics) or to treat opioid side effects (antihistamines, psychostimulants, laxatives, neuroleptics, antiemetics).

For neuropathic pain, some anticonvulsants, antidepressants, and opioid analgesics have been used but gabapentin has the strongest evidence base in cancer.

A small number of children, particularly those with extensive bony tumor metastasis and/or nerve involvement, may require more invasive pain management techniques. Radiotherapy, radionuclides, neuroaxial analgesia, and very rarely neurolytic blocks may be needed for pain control in these cases.

The value of adequate analgesia for children who undergo painful procedures cannot be overemphasized. For all patients, an opioid or a local anesthetic is needed to reduce the pain. EMLA cream provides a painless, well-tolerated method of local anesthesia/analgesia for punctures. The use of conscious sedation is highly recommended for the management of pain and distress associated with procedures such as BMA and LP.

Nonpharmacologic pain interventions should not be considered as a substitute for analgesics but as a means to increase the effectiveness of the pharmacologic management. They work best when introduced early in the course of the illness as a part of a multimodal treatment. When possible, children should also be offered the benefit of these interventions including physical, behavioral, and cognitive methods.

Pain management teams in hospitals could highly increase the quality of life for these children. Collaborative studies exploring the most effective pain management methods should be encouraged.

Treatment Results of Non-Hodgkin's Lymphoma in MECC Region

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Worldwide, lymphoma is the third most common cancer in children. In our country and in the Middle East region, it ranks second. In the last decade the survival rate has improved to 80% to 90%, and the primary treatment modality is chemotherapy in most cases.

The reports from the MECC region are given below.

Turkey: In the 70s chemotherapy protocols are based on cyclophosphamide, vincristine, and prednisolone. In 80s, LSA2-L2 and COMP protocols have been used. These chemotherapeutic protocols have achieved 50% to 60% survival compared with 20% to 30% with single agent chemotherapy. After 1990s high-dose methotrexate protocols were commonly used. Most of the centers preferred either LMB/LMT protocols or BFM protocols. Survival rates have improved to 75% to 85% with high-dose methotrexate protocols. A few center used total therapy B protocol.

Treatment results from Israel were similar to Turkish results. Most of the cases of B-cell lymphoma originated from the abdomen and jaw. Their results improved with use of the LMB regimen after 1986. Previously, they had used the BMC (cyclophosphamide + vincristine + methotrexate) protocol. Use of the LMB regimen achieved 96% survival rate that was 58% with BMC.

From Egypt, there is a report that NHL in childhood constitutes 16% of all malignancies. They achieved 60% survival rate with the use of the ifosfamide + methotrexate + etoposide protocol in advanced cases.

There are 2 reports from Jordan. One of them, which was published in 1986, included 24 patients. The treatment strategy was chemotherapy without RT. Only 50% of the patients survived. The other report was presented during the last non-Hodgkin lymphoma meeting in New York. The authors used the LMB86 regimen. This report described a small case series, with only 21 patients. Using the LMB86 protocol, the authors reported an excellent EFS and OS rate of 80%, though the follow-up time was short.

Kuwait presented their results in the last NHL meeting, though with a small number of patients. They studied 15 patients with B-cell lymphoma, using either the BFM or UKCCSG protocol. Two patients receiving the UKCCSG protocol had died.

One series from Saudi Arabia also included a small number of patients. It did not specify the chemotherapy protocol, but the survival rate was poor.

There is no treatment reports from the other countries such as United Arab Emirates, Syria, Iraq, Lebanon, and Cyprus.

Current practice is to use the protocols including high-dose methotrexate.

References:

1. Büyükpamukçu M, Sarıalioğlu F, Akyüz C, et al. Combined chemotherapy in 76 children with non-Hodgkin's lymphoma excluding Burkitt lymphoma. *Br J cancer*. 1987;56:625–628.
2. Kutluk T, Varan A, Akyüz C, et al. Clinical characteristics and treatment results of LMB/LMT regimen in children with non-Hodgkin's lymphoma. *Cancer Investig*. 2002;20:626–633.
3. Çavdar AO, Yavuz G, Babacan E, et al. Burkitt's lymphoma in Turkish children: clinical, viral [EBV] and molecular studies. *Leuk Lymph*. 1994;14:323–330.
4. Yavuz G, Cavdar A, Unal E, et al. Intensive short-duration chemotherapy in patients with childhood Burkitt's and B-cell non-Burkitt's lymphoma. *Hem J*. 2002;3:283.
5. Agaoglu L, Eryilmaz E, Devecioglu O, et al. Use of intensive chemotherapy for non Hodgkin's lymphoma—a single center experience. *Med Pediatr Oncol*. 2000;35:203.
6. Karadeniz C, Oguz A, Citak C, et al. Clinical characteristics and treatment results of pediatric B-cell non-Hodgkin lymphoma patients in a single center. *Ped Blood Cancer*. 2006;47:445.
7. Yaniv I, Fischer S, Mor C, et al. Improved outcome in childhood B-cell lymphoma with the intensified French LMB protocol. *Med Pediatr Oncol*. 2000;35:8–12.
8. Gad-el Mawla N, Hussein MH, Abdel-Hadi S, et al. Childhood non-Hodgkin's lymphoma in Egypt: preliminary results of treatment with a new ifosfamide-containing regimen. *Canc Chemother Pharmacol*. 1989;24(suppl 1):S20–S23.
9. Madanat FF, Amr SS, Tarawneh MS, et al. Burkitt's lymphoma in Jordanian children: epidemiological and clinical study. *J Trop Med Hyg*. 1986;89:189–91.
10. Jarrar M, Tawfeeq M, Mansour A, et al. Outcome of pediatric patients with Burkitt lymphoma in Jordan. *Ped Blood Cancer*. 2006;46:859.
11. Mittal R, Awadi AS, Shammari S, et al. Outcome of children with B-NHL, a single institution study from Kuwait. *Ped Blood Cancer*. 2006;46:862.
12. Thomas OA, Abdelaal MA, Ayoub DA. Childhood lymphoma in Saudi Arabia: experience at the King Khalid National Gard Hospital. *East Afr Med J*. 1996;73:343–345.

BFM-TR ALL 2000: First Turkish Multicentric Study in the Treatment of Pediatric Acute Lymphoblastic Leukemia

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With the aim of achieving standardization and repeating the successful results reported by the BFM Group on a nationwide basis, the first Turkish multicentric observation study BFM-TR ALL 2000 has been opened to patient accrual in January 2000. A modified ALL-BFM 95 protocol has been administered by reducing the methotrexate dose to 1 g/m^2, infused over 36 hours, to limit toxicity. Intermediate and high-risk patients received 1200 cGy cranial irradiation. Until January 2005, 1020 patients have been enrolled from 20 centers. Half of the patients were treated in 12 university hospitals and the rest in state and foundation hospitals. The centers participating showed a wide geographic distribution and reported 2 to 113 patients. The median age at diagnosis was 5 years, range 0.2 to 17 years, with 1.1% infants and 18.7% children older than 10 years. The male to female ratio was 1.2. The median WBC count was 14,000/μL, range 500/μL to 1,350,000/μL and 25% had counts over 50,000/μL, 1.1% being over 500,000. Initial CNS involvement was present in 4.1% and testicular involvement in 0.5% of the patients. Immunophenotyping showed T-ALL in 21%. According to ALL-BFM 95 criteria, 27% of the patients were standard, 56% intermediate, and 17% high risk. The reason of stratification to high risk was poor prednisone response (1000 or more blasts per cubic mm in the peripheral blood on day 8 of prednisone treatment) in 14.5% of the patients and no remission in the bone marrow on day 33 in 4.3% of the patients. Of the cases examined, 5% had t(9;22) and 3% had t(4;11). Remission was achieved in 96.5% of the patients. Totally, 16% of the patients died, 1.6% during induction, 0.6% due to nonresponse, 8.2% during first remission and the rest after relapse. Before relapse, 6.3% of the patients were lost to follow-up: 1.4% during induction and 5.1% in first remission. Relapse was observed in 10.3% of the patients, the bone marrow being involved in 7.5%, the CNS in 2.5%, the testis in 0.6%. The probability of EFS at 5 years was 70 ± 2% in the whole group, and 82 ± 3%, 72 ± 3%, and 45 ± 5% in the standard, intermediate, and high-risk groups, respectively. Females showed a trend for better prognosis with 74% versus 67% pEFS. This was most prominent in the high-risk group. Prognosis was closely related to age, with infants (pEFS 29%) and adolescents 10 to 15 years (pEFS 58%) and > 15 years (pEFS 50%) having the worst and children 1 to 6 years of age (pEFS 78%) having the best prognosis. An M3 bone marrow on day 15 was a statistically significant risk factor with 42% pEFS but it lost significance when evaluated according to risk group. Although there was a wide variation between the patient characteristics and treatment results of the participating study centers, the preliminary results of the first Turkish multicentric clinical study for pediatric ALL showed the feasibility of applying an intensive BFM-based chemotherapy protocol in a high number of centers in a standardized form. Besides an important number of patients being lost to follow-up, thus not receiving the full protocol, the primary cause of failure was the high rate of deaths in remission, the prevention of which should be the aim of continuing and future studies.

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Targeted Therapy

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Owing to the increasing understanding of the mechanisms relevant to the genesis of cancer, development of anticancer drugs is undergoing a paradigm change. The challenge of bringing new therapeutics to clinical application and registration now focuses on the molecular target expressed by the malignant cell rather than treatment of the histopathologic entity. Maximum tolerated dose (MTD) and response rate, however, are no longer the only decision-making end points of phase 1/2 trials. The new generation of compounds usually exerts only limited toxicity and, in most of cases, stabilizes the tumor rather than leading to massive reduction of tumor load. Therefore, additional end points different from those we are experienced to use for cytotoxic drugs need to be established to define subgroups of patients who will or will not profit from therapy.

Biomarkers serve as hallmarks for the status of tumor growth at a given time and change during the disease process. Their use for the detection of progressive disease or the definition of subpopulations of patients is not new. Increase of prostate-specific antigen during or after therapy for

example, points to disease progression in prostate cancer and the evaluation of estrogen and progesterone receptors is crucial to define optimum treatment of breast cancer. The first drug that was registered based on target expression was trastuzumab (Herceptin). It is important to note, that development of trastuzumab would have failed if it had been developed without knowledge of the HER-2 status. Another more recent example is the development of tyrosine kinase (TK) inhibitors directed against the epidermal growth factor receptor. Activating mutations in the TK domain of the receptor lead to enhanced TK activity in response to ligand binding and can predict response to therapy with TK inhibitors.

Thus biomarkers can guide us to define subgroups of patients whose tumors express a specific target and thus may have a high probability of response. They also provide a chance to allow proof of principle in early clinical trials to move rapidly to phase 3 and registration. Furthermore, biomarkers can help us to understand the mechanism of action. This is crucial because more and more molecular-targeted drugs enter combination trials before in depth knowledge of their efficacy and mode of action as a single drug as well as the investigation of potential resistance mechanisms.

With the help of our rapidly growing understanding of molecular biology of cancer it is thus crucial to define, evaluate, and validate additional biomarkers which at a later stage of clinical development may become surrogate markers and thus add to our conventional end points such as tumor shrinkage or disease progression. Despite our progress we are still in an early phase of biomarker development and whenever possible must aim to store material from study patients to be able to evaluate it at a later stage.