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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, FOOD AND DRUG ADMINISTRATION

Oncologic Drugs Advisory Committee Discussion on
FDA Requirements for Approval of New Drugs for
Treatment of Colon and Rectal Cancers

The FDA requirements for the approval of new drugs for the treatment of colon and rectal cancers were discussed at the Oncologic Drugs Advisory Committee meeting of April 19, 1988. The session began with presentations by Drs. Macdonald, Moertel, and Gunderson on different aspects of the treatment of colorectal cancer and ended with a committee discussion on the appropriate efficacy endpoints and control treatments.

Treatment of Advanced Colorectal Cancer
John Macdonald, M.D.

Although colon and rectal cancers are common malignancies, very few new agents have shown activity in Phase II studies. The objective response rates reported for intravenous administration of 5-fluorouracil in various doses and schedules have ranged from 8-85%. Many of these studies reported differences in survival favoring the responding patients. However, when the 5-FU treated group was compared to an untreated control group, there were no differences in overall survival. Because a comparison of survival in responding vs. non-responding patients is not acceptable evidence of efficacy, prospectively randomized Phase III studies are necessary to develop acceptable survival data.

Combination chemotherapy was the next step in the attempt to develop more effective treatment for advanced colorectal cancer. The objective response rates initially reported for methyl-CCNU and 5-FU combinations (\pm vincristine) ranged from 29-43%. In subsequent studies the response rate fell to 15-20%, suggesting that the combinations were not significantly better than 5-FU alone. Similarly, when the results of the MOF-streptozocin regimen were originally published, MOF-S appeared to be significantly better than MOF (objective response rates: 43% vs. 5%). However, in a larger Phase II study, the response rate with MOF-S was only 9%.

Since combination chemotherapy did not appear to be superior to single agent therapy with a fluorinated pyrimidine, the next step was to evaluate long-term continuous infusion of 5-FU or FUDR. Lokich reported response rates of 30-50% with a continuous intravenous infusion of 5-FU at a dose of 200-300 mg/m²/day. The Mid-Atlantic Oncology Group randomized 76 patients to standard bolus 5-FU at 500 mg/m² or to the continuous infusion regimen. The overall response rates were 8% for bolus 5-FU and 31% (including 5% CR's) for continuous infusion 5-FU. Although the median survival time was somewhat longer in the infusion arm, the difference was not statistically significant. Of interest was the change from myelosuppression and gastrointestinal toxicity with bolus

administration of 5-FU to the hand/foot syndrome with continuous infusion. The decreased myelosuppression with continuous infusion might permit the addition of a myelosuppressive drug at a full therapeutic dose. Cantrell administered 5-FU 300 mg/m²/day by continuous infusion for 12 weeks in combination with cisplatin 20 mg/m² weekly. The objective response rate was 63% with 47% partial and 16% complete responses. A Phase III study to confirm the remarkable activity of this regimen is underway.

Hepatic artery infusion of fluorinated pyrimidines in patients with liver metastases is another treatment approach under evaluation. The Central Oncology Group randomized 60 patients to intravenous or hepatic artery infusion of 5-FU. The response rates were 34% with hepatic artery infusion and 23% with systemic 5-FU. However, there were no differences in survival between the two treatment groups. Floxuridine (FUDR) has a higher hepatic extraction ratio than 5-FU and is the fluorinated pyrimidine of choice for hepatic artery infusion. The early Phase II studies of hepatic artery infusion with FUDR reported objective response rates of 54-88% and median survivals of 12-26 months. The response rates in subsequent studies have averaged between 60-70%. Several investigators evaluated hepatic artery infusion with FUDR and mitomycin in combination and reported response rates of 44-88%. In one study, 5 of 17 patients (25%) failing FUDR responded to the combination therapy.

Kemeny et al. randomized patients with liver metastases only to continuous intravenous infusion or to hepatic artery infusion of FUDR. The response rates were 50% with hepatic artery infusion and 20% with intravenous infusion. However, the incidence of extrahepatic metastases was greater in the hepatic artery infusion group (56% vs. 37%). Although there were no significant differences in survival, survival was difficult to assess because patients progressing on IV FUDR crossed over to hepatic artery infusion. In a similar study by the Northern California Oncology Group, the response rates were 42% for hepatic artery infusion and 9% for intravenous infusion. Again, the incidence of extrahepatic metastases was higher in the hepatic artery infusion group (50% vs. 22%) and the median survivals of both groups were identical. The major toxicities were chemical hepatitis, biliary sclerosis, and gastric ulcers with hepatic artery infusion and diarrhea with IV infusion. Kemeny analyzed the survival of patients with hepatic metastases, irrespective of whether they responded to treatment, and found that the degree of hepatic involvement at initial laparotomy correlated with survival. Because of the importance of this prognostic factor, well-designed, randomized Phase III studies are essential.

Ensminger analyzed the causes of death in a Phase II study of hepatic artery infusion at Michigan. Fifty-two percent of the patients were dead at 3 years and 78% of the deaths were from progressive extrahepatic disease while the hepatic metastases were controlled. In a group of matched controls who did not receive hepatic artery infusion,

86% died of hepatic failure. Therefore, the next treatment strategy might consist of hepatic artery infusion in combination with systemic therapy to control the extrahepatic disease.

A promising chemotherapeutic approach in advanced colorectal cancer is the administration of leucovorin in combination with 5-FU. Leucovorin is converted to 5,10-methylene-tetrahydrofolate which then stabilizes the FdUMP-thymidylate synthetase complex. Phase II studies using leucovorin doses of 60-500 mg/m² have reported objective response rates of 9-39%, and some of the responses occurred in patients refractory to 5-FU. An ongoing GITSG study is comparing 5-FU 500 mg/m²/day x 5 every 5 weeks, 5FU 370 mg/m² + leucovorin 200 mg/m² daily x 5 every 4 weeks, and 5-FU 425 mg/m² + leucovorin 20 mg/m² daily x 5 every 4 weeks. The Mayo Clinic and NCCTG are comparing 5-FU alone, 5-FU + low-dose leucovorin, 5-FU + high-dose leucovorin, intermediate-dose methotrexate followed by 5-FU and leucovorin, methotrexate and 5-FU, and 5-FU and cisplatin. The results of these studies should be available in the near future.

PALA is another biochemical modulator that is under evaluation. By inhibiting L-aspartate transcarbamylase, PALA inhibits an early step in pyrimidine biosynthesis. This decreases the availability of UDP and UTP and increases the incorporation of FUTP into DNA. Ardalan reported on a randomized Phase I-II study of a short term infusion of high-dose 5-FU with or without PALA in patients with advanced pancreatic and colorectal cancers. In the combination arm there were 2 complete (10%) and 8 partial (38%) responses for an overall response rate of 48%. The response rate in the 5-FU arm was 10%.

Adjuvant Therapy of Colon Cancer
Leucovorin and Fluorouracil for Advanced Colon Cancer
 Charles Moertel, M.D.

Approximately 100,000 Americans each year are potential candidates for surgical adjuvant therapy. Because of these numbers, even a modestly effective treatment could save many thousands of lives each year. However, because many of these patients will not have a recurrence, excessive toxicity could have severe consequences.

The national end result statistics have shown a steady improvement in 5-year survival by stage over a 30 year period. However, the apparent improvement in outcome may actually represent a trend in improved pathology staging, the so-called "stage migration" phenomenon. Therefore, any comparison of surgical adjuvant therapy today to a historical control is likely to result in a positive study whether the treatment is effective or not. A cursory review of the gastrointestinal surgical adjuvant literature will reveal that historically controlled studies are always positive. On the other hand, a randomized study does not ensure validity. For example, a GITSG study in poor prognosis gastric cancer randomized patients to either surgery alone or to adjuvant

therapy with 5-FU and methyl-CCNU. The adjuvant treatment was reported to be a breakthrough with a striking and significant 15% improvement in 5-year survival. However, in an identical study conducted by ECOG, the survival curves for the treatment and control groups were superimposable. In addition, the difference in survival between the two studies was 15%. Fifteen percent of the GITSG patients were not included in the analysis because they were ineligible or cancelled. Sixteen percent of the ECOG patients were excluded because of similar quality control problems. As a generous rule of thumb, if more than 10% of patients entered on a study are lost to analysis because of quality problems, the study should be considered unreliable.

The initial trials of surgical adjuvant therapy in colorectal cancer utilized thiotepa. The University Surgeons Group study was completely negative. The 5-year survival in the Veterans Administration study was significantly better in the control arm, illustrating a potential hazard of ineffective surgical adjuvant therapy. Because of their activity in advanced disease, subsequent adjuvant studies evaluated 5-FU and FUDR. Lee et al. administered two courses of 5-FU immediately after surgery and reported a highly significant survival improvement in patients with Dukes B and C disease compared to historical controls. A randomized study conducted by the VASAG compared the same treatment to surgery alone and found no difference. The VASAG group conducted a second randomized study comparing one year of 5-FU to no further treatment and found a slight, but non-significant difference. The COG used a more toxic dose of 5-FU and also found no significant differences. Dr. Blokhina in the U.S.S.R. used a gentle 5-FU regimen and found that their control group did slightly better than the treated group. A large placebo-controlled study conducted in Sweden demonstrated that adjuvant therapy with 5-FU was worthless. The Veterans Administration group also evaluated FUDR in a study with a very large patient accrual and found that the control group did better than the treated group. The Rousselot technique consists of intraluminal 5-FU at the time of surgery followed by systemic 5-FU postoperatively. The initial study utilized a historical control group and reported a striking improvement in the treated group. However, two subsequent randomized studies were negative. The overwhelming evidence is that the fluorinated pyrimidines are ineffective as surgical adjuvant therapy in colorectal cancer.

Subsequent adjuvant trials evaluated combination chemotherapy, immunotherapy, or combination chemotherapy plus immunotherapy. In a transplanted colon carcinoma model in nude mice, surgery plus chemotherapy with 5-FU and methyl-CCNU improved survival and cure rates compared to surgery or chemotherapy alone. Similar animal model results were observed with MER-BCG. Therefore, a GITSG study randomized patients to no further treatment, methyl-CCNU + 5-FU (MF), MER-BCG, or MF + MER-BCG. Unfortunately, the clinical trial did not reproduce the animal model results and there were no survival differences between the treatment groups. The Veterans Administration group also evaluated the MF combination and found no benefit.

With these negative results, it is surprising that the MOF regimen is being promoted as effective adjuvant therapy for colorectal cancer. The survival improvement reported for the NSABP C-01 study did not quite reach a p value less than 0.05. The apparent spread of the survival curves was enhanced by the semi-log plot and the actual percentage improvement was quite small. The only significant finding in the study was an improvement in survival in the BCG arm ($p=0.03$). The investigators decided that the result was explained by deaths that were unrelated to cancer. Because 22% of the patients randomized to chemotherapy were either ineligible, lost to follow-up, or never received treatment, serious questions must be raised about the validity of the results. The Southwest Oncology Group compared MF + BCG, MF, and no further treatment. The best survival was in the control group and the worst survival was in the MF + BCG group.

A major question concerns the contribution of methyl-CCNU to this combination. The ECOG study randomized approximately 800 patients to methyl-CCNU + 5-FU or to 5-FU alone. Because there was no benefit to the combination therapy and because of the substantial risk of leukemia and renal failure associated with methyl-CCNU, it appears to be medically inappropriate to continue to expose colon cancer patients to the drug.

Levamisole is an antihelminthic drug with immunomodulatory properties. In a Belgian study, adjuvant therapy with levamisole was compared to placebo. Although the study was very small, there was a significant advantage for levamisole therapy. The NCCTG then randomized Dukes B₂ and C patients to no treatment, levamisole alone, or levamisole + 5-FU. The study was of high quality with less than 3% of patients lost to analysis, and the prognostic factors and patient characteristics were well-balanced. The recurrence rates in the levamisole and levamisole + 5-FU arms were significantly lower, especially in Dukes C patients. Similar improvements in overall survival approached statistical significance and survival was significantly better in the Dukes C patients. A confirmatory intergroup study recently completed patient accrual and the results should be available in approximately 3 years. A small U.K. study compared no treatment to 5-FU and to 5-FU + levamisole and found a highly significant survival advantage for the 5-FU + levamisole arm.

Taylor reported a reduction in hepatic metastases and a significant improvement in overall survival with a 7-day portal vein infusion of 5-FU immediately after resection. However, the postoperative complication rates in the treatment and control groups were excessively high and the survivals were quite low compared to other contemporary series. The results of confirmatory trials by the NCCTG and the NSABP should be available in 1-2 years.

Biochemical modulation is also being considered in the adjuvant setting. In advanced colorectal cancer, the NCCTG compared 5-FU + PALA,

nodal involvement and extension beyond the wall, the risk was additive, varying from 40-70%. In addition, in node-negative patients the incidence of total failure and pelvic recurrence correlated significantly with the degree of extension beyond the wall. There was also a similar, but not significant, trend in node-positive patients. Therefore, the farther the lesion extends beyond the wall and the narrower the margin of normal tissue the surgeon can remove, the higher the incidence of local recurrence. The high incidence of local recurrence in rectal cancer is a reflection of anatomical limitations that are not a factor in colon cancer. Because pelvic recurrences can cause a great deal of morbidity with symptomatology, the primary endpoints of adjuvant therapy in rectal cancer should include not only relapse-free and overall survivals but also local recurrence.

Adjuvant radiation therapy has been administered preoperatively or postoperatively. Evidence that rectal cancer is radiosensitive is available from preoperative and primary radiotherapy series. In the preoperative series from Yale and Oregon, the percentage of patients having no remaining tumor in the specimen varied from 10-22%. In the Princess Margaret Hospital series of patients who had clinically mobile lesions but either refused surgery or were poor medical candidates, the 5-year survival with radiation therapy alone was 38%. Low-dose (500-2000 rad) preoperative radiotherapy does not reduce the incidence of local recurrence.

In a randomized EORTC study of preoperative irradiation, a dose of 3450 rad in 230 rad fractions (equivalent to 4000 rad in 180 rad fractions) significantly reduced the incidence local recurrence compared to surgery alone ($p=0.001$). The decrease in local recurrences resulted in a significant improvement in disease-free survival ($p=0.05$) but did not translate into a significant improvement in survival ($p=0.12$). In a 1986 update, the improvement in local recurrence-free survival persisted ($p=0.002$) and had translated into an overall survival benefit ($p=0.03$). Because the time between first recurrence and death in rectal cancer can range from one to two years, longer follow-up is generally required before an improvement in disease-free survival can translate into an improvement in survival. The unpublished EORTC study is the only randomized trial of preoperative radiotherapy with significant improvements in local recurrence, disease-free survival, and survival.

A non-randomized study at the Massachusetts General Hospital compared local recurrence at three years in a group of patients treated with surgery alone to a subsequent group of patients that received postoperative irradiation. Pelvic failure was reduced in the majority of patients receiving postoperative radiotherapy. In a 1987 update, the node negative patients who received postoperative radiotherapy still had a significantly lower incidence of local recurrence. Although there was also a reduction in local recurrence in patients with positive nodes, 20-30% had recurred despite postoperative irradiation. When 5-year

5-FU + thymidine, 5-FU + levamisole, and the MOF-strep regimen. There were no significant survival differences between the treatment groups. Five different 5-FU + leucovorin combinations have been compared to 5-FU in controlled trials in patients with advanced disease. Roswell Park, GITSG, and the City of Hope used very high doses of leucovorin, 500 mg/m², by 2-hour and 24-hour infusions. The Machover regimen used a slightly lower dose of leucovorin given in a 5-day course. Because of cost considerations, both the GITSG and NCCTG groups also looked at much lower doses of leucovorin. Although the studies reported highly significant improvements in response rates, only the Princess Margaret study reported a significant improvement in survival (p=0.05). However, the Canadian study used a very low dose of 5-FU in the control arm.

The most recent NCCTG study compared a 5-day course of 5-FU alone to 5-FU + cisplatin, 5-FU + intermediate-dose methotrexate with leucovorin rescue, 5-FU + low-dose methotrexate, 5-FU + high-dose leucovorin, and 5-FU + low-dose leucovorin. A total of 429 patients were randomized and only 1.9% were inevaluable. The dose-limiting toxicity of 5-FU and 5-FU + cisplatin was severe leukopenia in approximately half of the patients. Unlike the RPMI study using weekly leucovorin + 5-FU, diarrhea with the 5-day combinations was no different than with 5-FU alone. The dose-limiting toxicity of the leucovorin regimens was stomatitis, and the same degree of biologic modulation of toxicity occurred with high and low doses of leucovorin. The highest response rates were observed with 5-FU + low-dose leucovorin and were significantly higher than with 5-FU alone. The 5-FU + low-dose methotrexate arm was also significantly better than the 5-FU arm. Time to progression was significantly longer in the leucovorin arms than in the 5-FU arm (p=0.007). Survival in both 5-FU + leucovorin arms was significantly better than with 5-FU alone (p=0.02 and 0.03), and there were also significant improvements in weight gain and performance status. Because of these promising results in patients with advanced disease, the NCCTG has initiated a study in the surgical adjuvant setting. Patients will be randomized to 5-FU + leucovorin, 5-FU + leucovorin + levamisole, or no treatment. There will also soon be an intergroup trial involving ECOG and SWOG.

Adjuvant Therapy of Rectal Cancer

Leonard Gunderson, M.D.

Over 40,000 new cases of rectal cancer are diagnosed annually. While surgical resection of early stage disease is highly successful, there is a substantial risk of local recurrence and/or distant metastases in patients with lesions extending beyond the rectal wall, invading perirectal tissues, or metastasizing to lymph nodes. Data generated by Gilbert in 1976 demonstrated that local recurrences produced by far the highest percentage of symptoms from rectal cancer. In patients with positive nodes and tumor confined to the bowel wall the risk of local recurrence was 20-30 percent. In patients with negative nodes and tumor extending beyond the wall, the risk was 20-35%. In patients with both

survival was analyzed, there was a suggestion of an improvement in survival in patients with a single high-risk factor (extension beyond the wall, B₂ or B₃ subsets, or node positive confined to the wall). Survival in these patients after radiotherapy was 70-75% compared to 35-47% with surgery alone. However, in patients with both high-risk factors, the C₂ and C₃ subsets, there was little difference in 5-year survival. The reason for this was the high incidence of systemic failure, approximately 50% in the C₂ and C₃ groups combined (60% in C₃). Therefore, future clinical trials may require more aggressive therapy in node positive patients.

In the NSABP R-01 study, 555 patients with extension beyond the wall and/or positive nodes were randomized to observation (184), adjuvant chemotherapy with MOF (187), or postoperative radiotherapy (184). However, only 154 of the chemotherapy patients and 158 of the radiation patients actually received the randomized treatment. In those patients who were randomized to receive radiotherapy, local recurrence decreased from 25% with surgery alone to 16% with surgery and irradiation ($p=0.06$). The reduction in local recurrence with radiotherapy did not result in an improvement in survival or disease-free survival.

Chemotherapy alone as adjuvant treatment for rectal cancer has also failed to prolong survival. In the ECOG study there was no improvement in overall survival with 5-FU after surgery. Only on exploratory subset analyses was there a suggestion of a survival benefit. There was also no improvement in survival in the GITSG study comparing 5-FU + methyl-CCNU to no further treatment after surgery. In the NSABP study, there was a survival benefit from chemotherapy only in the subset of young males. However, in a recent update of the NSABP study, survival ($p=0.05$) and disease-free survival ($p=0.006$) were significantly better in the chemotherapy arm than in the surgery only control arm. When the patterns of initial failure were analyzed, chemotherapy appeared to result in a non-significant but lower incidence of local and distant recurrences.

The GITSG conducted the initial study of combined modality adjuvant therapy. The four-arm study randomized patients to no further treatment after surgery, postoperative radiation (4000-4800 rad), chemotherapy, or postoperative radiation (4000-4400 rad) plus chemotherapy. When the data was originally published in 1985, there was a statistically significant improvement in disease-free survival in the combination group compared to the surgery only group. In a 1986 update, there was also an improvement in overall survival ($p=0.005$). When the patterns of initial failure were analyzed, the best group was irradiation plus chemotherapy. When local-regional failure was analyzed, there was absolutely no difference between the chemotherapy and surgery groups. In fact, the local recurrence rate was higher in chemotherapy arm. Radiation did significantly reduce the incidence of local recurrence ($p=0.04$). The only group of patients that appeared to have a significant decrease in local and regional recurrence was the radiation plus chemotherapy group.

When the distant failure rate was examined, no treatment arm appeared to significantly lower the incidence of metastatic disease.

The Mayo/NCCTG study randomized patients to postoperative radiotherapy or to chemotherapy with 5-FU and methyl-CCNU before and after radiotherapy. The maximum radiotherapy dose of 5000 rad was also higher than in the GITSG study. In 1987 there was a significant improvement in disease-free survival in favor of the combined modality group ($p=0.02$). In a 1988 update, the disease-free survival improvement was still present and the p value for a non-significant improvement in survival had dropped from 0.2 to 0.14. When the initial sites of failure were analyzed, the improvements with radiation plus chemotherapy had occurred both locally ($p=0.02$) and systemically ($p=0.05$). Combined therapy can be given safely if lateral fields are used in conjunction with AP-PA fields. The lateral fields can spare the anterior lining of the small bowel. At M.D. Anderson, the incidence of small bowel obstruction requiring surgery with lateral fields was 10-12% compared to 5% after surgery alone. More sophisticated multiple field techniques appear to lower the incidence of small bowel obstruction to that of surgery alone. With a minimum follow-up of two years, the incidence of severe treatment related enteritis in the Mayo/NCCTG study was less than 5% and was equivalent in the radiotherapy and radiotherapy plus chemotherapy arms.

In conclusion, the primary efficacy endpoints for adjuvant therapy of rectal cancer are pelvic recurrence, disease-free survival, and overall survival. The only preoperative radiotherapy study with an improvement in all three endpoints is the unpublished EORTC trial. Additional studies will be required to confirm the results. Randomized and non-randomized studies of postoperative radiotherapy have reported reductions in local recurrence but no improvements in overall survival. Since there is only one positive trial, chemotherapy alone does not appear to have an important therapeutic effect. Two studies of chemotherapy and postoperative radiation, the GITSG and NCCTG trials, have demonstrated the superiority of combined modality therapy over radiotherapy alone. Although a significant improvement in survival was not seen in the NCCTG study, the reduction in distant failure and the improvement in disease-free survival should translate into an improvement in overall survival with further follow-up. Future clinical trials should look at optimal ways of combining radiation and chemotherapy, should explore different drugs, routes and timing, and should determine whether adjuvant therapy is necessary in all node negative patients. The ongoing NCCTG/intergroup trial addresses two of the important issues. The study involves a 2 x 2 stratification in which half the patients will receive methyl-CCNU + 5-FU and half will receive 5-FU alone. Half will receive protracted chemotherapy during the entire sequence of radiation therapy while half will receive bolus 5-FU at weeks 1 and 5. Another interesting question is whether 5-FU plus low-dose leucovorin can be administered concomitantly with irradiation, thus starting both local and

systemic treatments simultaneously. The Mayo Clinic and the NCCTG are piloting a study in patients with advanced disease.

Committee Discussion

After the presentations, the committee was asked to address a series of questions concerning the appropriate efficacy endpoints and control treatments for clinical trials in colorectal cancer:

1. "Are there well controlled studies showing that chemotherapy benefits patients with advanced metastatic colon and rectal cancer? If so identify the chemotherapy, the well controlled studies and the efficacy endpoints on which your answer is based."

Dr. Macdonald answered that if benefit was defined by reproducible response rates which frequently result in palliation of symptoms, then 5-FU, with a response rate of 10-20%, could be considered a not very adequate palliative therapy. A reasonable regimen would consist of a 5-day course of 500 mg/m²/day repeated every 4-5 weeks. However, most studies in advanced colorectal cancer have not demonstrated an improvement in survival. Survival is obviously an important endpoint and recent studies with 5-FU plus leucovorin suggest that it may be possible to improve survival. Hepatic artery infusion may also increase survival slightly and could be used as a building block for a more effective regimen.

Dr. Moertel recommended that the leucovorin plus 5-FU combination be the standard against which future treatments of advanced colorectal cancer should be compared. In the Mayo/NCCTG study, the combination was superior to 5-FU, even though 5-FU was escalated to equitoxic doses. Therefore, 5-FU plus drug "X" should be at least as good as 5-FU plus leucovorin. In advanced rectal cancer, the endpoints and the regimens are the same. In studies combining colon and rectal cancer, neither colon nor rectum has been found to be a significant prognostic determinant for response or survival.

2. "At present, the FDA and its ODAC believe that a favorable effect on survival or quality of life in well controlled studies is an appropriate basis for approval of a new cancer drug for advanced metastatic colon and rectal cancer. Are there other efficacy endpoints that could provide sufficient basis for approval in the absence of data showing a favorable effect on survival or quality of life or in the absence of any data on survival or quality of life? For example, is there data showing that objective response rate, response duration or time to progression are surrogates for survival or quality of life in patients with metastatic cancer of the colon and rectum? Does the answer to this question differ for the typical cytotoxic drugs compared to drugs with little or no toxicity? Are there any instances where randomized controlled clinical studies are not necessary?"

Dr. Moertel answered that response rates are not a satisfactory surrogate for quality of life or survival. In the Mayo/NCCTG study, improvements in performance status and weight gain without edema were easily assessable measurements of quality of life and would be convincing endpoints in a randomized controlled study. A trial with a highly significant improvement in quality of life and immature survival data should be considered. There are no instances where randomized controlled studies are not necessary.

3. "Are there well controlled studies showing that adjuvant chemotherapy benefits patients with colon cancer? If so, identify the chemotherapy, the well controlled studies and efficacy endpoints on which your answer is based."

Dr. Moertel answered that there are no studies yet which demonstrate that adjuvant chemotherapy benefits patients with colon cancer. Therefore, the best standard therapy would be surgery alone and a new treatment would have to be better than surgery.

4. "At present, the FDA and its ODAC believe a favorable effect on survival in well controlled studies is an appropriate basis for approval of a new cancer drug for adjuvant therapy of colon cancer. Is a favorable effect on DFS without evidence of a favorable effect on survival sufficient basis for approval? Is a favorable effect on DFS without assurance that there is no adverse effect on survival sufficient basis for approval? If DFS without an effect on survival is the basis for approval, what consideration, if any, should be given to the toxicity and duration of administration of the adjuvant chemotherapy?"

Dr. Macdonald answered that because patients who recur will inevitably die of their disease, an improvement in disease-free survival should translate into a survival advantage. Dr. Moertel stated that because the date of recurrence is soft, one should wait until the survival data is available. Dr. Capizzi noted that at present there is no salvage therapy which is likely to obscure a potential survival difference between two adjuvant therapies.

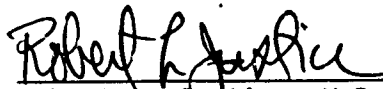
5. "Answer questions #3 and #4 above concerning adjuvant chemotherapy of rectal adenocarcinoma."

Dr. Moertel stated that the answer in rectal cancer is not as clear as in colon cancer. Although the GITSG study was stopped at 50% of planned accrual and had many ineligible patients and major radiation therapy deviations, the survival advantages were impressive. The NCCTG study suggests a benefit in interval to progression and local recurrence and when mature may demonstrate an improvement in survival.

Dr. Gunderson noted that because a local recurrence in rectal cancer is almost always symptomatic, local recurrence is a reasonable endpoint. However, it is still a soft endpoint and an improvement in survival would be preferred. Although combined modality therapy with postoperative irradiation and methyl-CCNU plus 5-FU was positive in the GITSG and Mayo/NCCTG trials, the components producing the positive results are still unclear. Because chemotherapy has had no impact on local recurrence, the control treatment in future studies should consist of a radiation plus chemotherapy combination. A recommendation regarding a specific chemotherapy regimen should be delayed until the results of the intergroup study are available. If 5-FU plus methyl-CCNU with postoperative irradiation proves to be superior to 5-FU plus irradiation, then a new treatment (e.g. 5-FU plus drug "X") should be at least as good as MF plus radiotherapy.

6. "In advanced metastatic colorectal cancer, if you had a drug that produced a good response rate and the drug was non-toxic, would you approve the drug without survival data just on the basis of the response rate?"

Dr. Moertel answered that if nothing else happens, tumor shrinkage alone should not be sufficient for approval.


Robert L. Justice, M.D.