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Appendix 2:
Osteonecrosis in Cancer Patients

Zometa® (zoledronic acid) Injection

and

Aredia® (pamidronate disodium) Injection

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1 Executive summary

Incidence of osteonecrosis (ON) in cancer patients and main risk factors for the disorder were evaluated based on literature review and an epidemiological study performed in the UK General Practice Research Database (GPRD).

- Literature-based evidence:
  - ON has been frequently described in cancer patients in association with cancer treatment: radiotherapy or chemotherapy with and without corticosteroids.
  - Systemic corticosteroid therapy is the most common risk factor for non-traumatic ON. Other include alcohol abuse, sickle cell disease, Gaucher disease, dysbaric conditions, coagulopathies, hyperlipidemias, radiotherapy, anti-cancer chemotherapy, chronic liver disease, pancreatitis, HIV infection and pregnancy.
  - Fungal, bacterial and viral infections, trauma and local anesthesia are common risk factors for ON of the jaws.
- Population-based evidence:
  - Methods: A source population of 5,597,148 persons (8,998,314 person-years) 20 to 84 years of age with information recorded in GPRD during the period of 01-01-1994 to 31-12-2001 was identified as the general population cohort and used to derive three additional cohorts: cancer patients, systemic corticosteroids users and systemic corticosteroids non users. Incidence rates of ON were calculated for all these cohorts.
  - Results: The estimated incidence of ON of all sites among the cancer cohort was 1.31 per 10,000 person-yrs (95% CI: 0.72-2.21). For comparison, in general population the incidence rate was estimated to be 0.31 per 10,000 person-yrs (95%CI: 0.27-0.35). The estimated incidence rate of ON among corticosteroids users was 0.99 per 10,000 person-yrs (95%CI: 0.74-1.31). When compared to the risk among non users, the relative risk for corticosteroid use was 3.96 (95%CI: 2.60-5.39).
- Conclusions:
  - Systemic corticosteroid therapy is a strong risk factor for ON.
  - ON is a well documented complication of anti-cancer therapy. In GPRD in the United Kingdom, the incidence of ON in cancer population is over 4 times higher than in general population. However, since data on anti-cancer chemotherapeutic drugs and on IV bisphosphonates are not complete in this out-patients database, these risk factors cannot be assessed.
  - The jaw bones, unique among skeletal structure because of the presence of the teeth, are frequently subject of local infections, which is considered to be an additional main risk factor for ON in this location.

2 Background

This epidemiological review has been prepared to support actions in response to the MHRA request regarding osteonecrosis (ON) in association with pamidronate.

Osteonecrosis (avascular necrosis of bone, ischemic necrosis or osteochondritis dissecans) is the death of bone that results in the collapse of the architectural bony structure, leading to bone pain, destruction and loss of function. It is considered to be not a specific disease entity but the final common pathway of a number of conditions leading to an impairment of the blood supply to the bone. The most commonly affected sites are the femoral head, the humeral head and the knees (femoral condyles and proximal tibia) (Assouline-Dayan 2002, Pavelka 2000).

3 Objectives

The main objective of this report is to review and summarize data on the incidence of ON in cancer patients. In addition, the risk factors of ON, especially those most relevant to cancer patients, are analyzed.

4 Methods

4.1 Literature search

An electronic literature search of English-language studies was conducted through the MEDLINE database from 1970 to the present time to obtain all published studies relating to the incidence of ON and specifically ON of the jaws among cancer patients and the risk factors for this condition. Special attention and focus was placed to the occurrence of this disorder among patients with the breast and multiple myeloma malignancies.

Key words included “osteonecrosis” combined with: “cancer patients”, “jaws”, “maxilla“, “mandible”, “breast cancer”, “multiple myeloma” and “risk factors”.

Bibliographic references of retrieved articles were reviewed to identify additional studies not captured by the initial search. Case series and case reports publications were included when they were considered to provide relevant information.

4.2 Population-based database study

4.2.1 Source population and study cohorts

The General Practice Research Database (GPRD) in the United Kingdom contains computerized medical information entered by participating general practitioners (Garcia Rodriguez 1998). Currently the database contains data on over 5.5 million patients. The recorded data includes patient demographics, symptoms, medical diagnoses from outpatients’ visits, referrals to consultants, hospitalizations, and drug prescriptions issued.

The study population was derived from all persons from 20 to 84 years of age registered in GPRD and identified during the period between 01-01-1994 to 31-12-2001. The following three cohorts of patients were drawn from this general population cohort:

- cancer cohort; patients with a diagnosis of a cancer,
- patients on systemic corticosteroid therapy,
- general population with systemic corticosteroids users excluded

All members in the general population cohort and the three cohorts above were followed-up until the earliest of the following endpoints: 1) diagnosis of ON; 2) death; or 3) end of the study period.

The following codes were used for the diagnosis of cancer: ICD-8 codes 1400 through 1738 plus 1740 through 2090 plus 971 for isotope therapy and 972 for cancer chemotherapy.

4.2.2 Case ascertainment

Among the four cohorts members potential cases were identified through an automated search for READ, OXMIS and ICD-8 codes listed in Table 8-1. In addition to assure identification of all cases, codes for mandibulectomy and maxillectomy (Table 8-2) were used for the cancer cohort.

Computerized patient profiles of potential cases identified in the cancer cohort were manually reviewed. All patients identified using codes listed in Table 8-1 fulfilled the case criterion (diagnosis of ON). The search performed with codes for mandibulectomy and maxillectomy revealed 13 additional potential cases. However, none of them fulfilled the case criterion. Therefore, only codes listed in Table 8-1 were used for the automated search.

4.2.3 Person-time calculation

Person-years of follow-up were calculated as follows:

- for general population cohorts: from time of the beginning of the study period to the earliest endpoint;
- for cancer cohorts: from time of the diagnosis of cancer to the earliest endpoint; and
- for corticosteroids users cohort: from time of the first systemic corticosteroid prescription to the earliest endpoint.

4.2.4 Analysis

Incidence rates of ON were calculated using person-time at risk as denominator. Ninety-five percent confidence intervals were computed on the basis of a Poisson distribution of case counts (Breslow and Day 1987). The Stata program was used to obtain estimates of rate ratios (STATA 1998).

5 Results

5.1 Literature-based evidence

From the initial search of “osteonecrosis in cancer patients”, two hundred and thirteen (213) published articles were identified by the described method. Neither the malignancy specific searches on osteonecrosis in breast cancer and multiple myeloma nor the search with the key words “osteonecrosis” combined with “jaws”, “maxilla” or “mandible” retrieved additional

articles. When the key words "osteonecrosis" and "risk factors" were combined, three hundred and two (302) publications were identified, some of them overlapping with the results of the initial search.

Twenty individual publications providing data in relation to the incidence of ON in cancer patients and/or risk factors for the condition were selected for review. Most of the publications appeared in the form of case-report or case-series reports. Although they could not be used for incidence estimation, they were included as they provided key information on the occurrence of the condition and its association with potential predisposing factors.

5.1.1 Incidence of ON in cancer patients

There are few data in literature on the incidence of ON. A large epidemiological study in 1989 reported 2,500-3,300 new cases of non-traumatic ON per annum in Japan (Ninomiya 1989). The number of new cases of ON of the femoral head detected annually in the USA is estimated to be 15,000 (Pavelka 2000). Bouquot (2003) reported the jaw ON prevalence rates relative to pain-related, biopsied cases in the population of northern West Virginia, USA. They found an annual prevalence rate of 0.2/1,000 population (females = 0.5/1,000; males = 0.05/1,000; females 24-75 years of age = 0.5/1,000; females 75+ years of age = 2.8/1,000).

Data on incidence of ON in cancer patients are scarce. ON is estimated to occur in 1 -10% of patients with lymphomas and acute leukemias treated with corticosteroids (Kozuch et al 2000). Cook et al (2001) reported the prevalence of ON of 3.8 % with a 3 year actuarial risk of 6.3% in patients treated with chemotherapy for testicular tumors. However, a careful search of the literature did not reveal any data on incidence of ON in general cancer population. To provide this information population-based study in GPRD was performed (see below).

5.1.2 Risk factors for ON

Non-traumatic ON occurs most commonly as a complication of corticosteroid therapy. In Japan, 34.7% of ON is thought to be corticosteroid induced, 21.8% due to alcohol abuse and 37% idiopathic (Ninomiya 1989). Western studies of ON have also highlighted systemic corticosteroids as the most common cause of ON (Coombs and Thomas 1994). Estimates of frequency of corticosteroid induced ON range from 3 to 4 percent to over 25 percent (Mankin 1992). Hurel and Kendall-Taylor (1997) found that the risk of ON increases with cumulative total dose of corticosteroids. The lowest reported total dose of corticosteroids was 480 mg in one month. The period of time before the onset of symptoms varies. Gogas and Fennelly (1996) found that ON could appear as early as 2 months or as late as 78 months after initiation of corticosteroid therapy. However, the condition may become symptomatic several years after completion of treatment (Coombs 1994, Gebhard 2001). Patients with systemic lupus erythematosus (SLE) have a 10% risk of developing ON after 3 years of symptomatic disease and 30% risk after 10 years. However, steroid treatment is not the only etiological factor of ON in SLE, as on occasions patients may have ON as their presenting feature for the disease with no history of previous steroid treatment. Ten percents to 40% of renal transplant patients who receive high doses of steroids develop ON. Other risk factors include sickle cell disease, Gaucher disease, dysbaric conditions, coagulopathies, hyperlipidemias, chronic liver disease, pancreatitis, pregnancy, HIV infection, and radiation therapy (Pavelka 2000, Wolfe 2000).

ON has been described as a complication of chemotherapy, especially where it includes intermittent high dose corticosteroids. Several reports have been published recently describing ON in patients treated with combination chemotherapy for testicular tumors who received corticosteroids as part of the anti-emetic regimen (Kozuch 2000, Virik 2001). A case of ON following chemotherapy with short term corticosteroids (total dose of dexamethasone 200mg) for small cell bronchogenic carcinoma has also been reported.

Chemotherapeutic drugs themselves have also been causally implicated in ON. Harper, Trask and Souhami (1984) described multisite ON in a patient who received vinblastine and bleomycin for a testicular embryonal carcinoma. Obrist, Hartmann and Obrecht (1978) reported ON of the humeral head after cyclophosphamide, methotrexate and 5-fluorouracil for breast carcinoma. Marymont and Kaufman (1986) described ON of the femoral condyles of both knees in a woman receiving adriamycin, methotrexate, and 5-fluorouracil for breast carcinoma.

The jaw bones, mandible and maxilla, are unique among skeletal structures because of the presence of the teeth - frequent route of local infections. Another specificity of this location is repeated use of local anesthesia for routine dental restorative procedures. Vasoconstrictors typically contained in anesthetics can severely decrease regional blood flow increasing risk for ON (Bouquot and McMahon 2000). Therefore, main risk factors for ON of the jaws differ slightly comparing to the rest of the skeleton and include fungal, bacterial and viral infections (Pogrel and Miller 2003), trauma and local anesthesia. Sung et al (2002) presented a case of ON of the maxilla in a 48-year old woman with acute myelogenous leukemia after chemotherapy (idarubicin, cytarabine) without corticosteroid administration. In this immunocompromised patient ulcerations associated with oral herpes simplex virus provided enough breach of the mucosal integrity to allow for the normal microflora of the oral cavity to invade the maxilla and cause infection leading to ON. Napoli and Donegan (1991) described a case of aspergillosis leading to ON of the maxilla in an immunocompromised patient with acute myelogenous leukemia. Schwartz (1982) described two cases of ON of the jaws after cancer chemotherapy. Both patients suffered from Hodgkin's disease. One patient was treated with CCNU, procarbazine and prednisone, second one with MOPP (mechlorothamine, vincristine, procarbazine and prednisone). Both were edentulous, one had an oral herpes simplex infection. The author discussed susceptibility of the jaw bones to severe infections in cancer patients that may lead to bone involvement including ON.

5.2 Population-based evidence

5.2.1 Incidence of ON in cancer patients

A total of 5,597,148 persons (8,998,314 person-years) 20 to 84 years of age with information recorded in GPRD during the period of 01-01-1994 to 31-12-2001 were identified. From this general study population a cohort of patients with a diagnosis of cancer (total 106,477 person-yrs) formed the basis for the estimations of the incidence of ON among cancer patients as described in the corresponding methods section.

Fourteen (14) patients with ON were identified among the cancer cohort . The incidence was estimated to be 1.31 per 10,000 person-yrs. For comparison, two hundred seventy eight (278) cases of ON were found in the general study population. The estimated incidence of ON was

0.31 per 10,000 person-yrs. (Table 8-3). The estimated incidence rates of ON among the cancer cohort and among the general population cohort by age group are displayed in Table 8-4 and Table 8-5, respectively.

5.2.2 Risk of ON in systemic corticosteroids users

The initial study population described above was used to form two additional cohorts: a cohort of systemic steroids users (502,817 persons-yrs) and a cohort of steroids non users, i.e. general population with systemic corticosteroids users excluded (7,866,530 person-yrs). Fifty (50) and one hundred ninety eight (198) cases of ON, respectively, were identified among these cohorts. The estimated relative risk of ON in systemic corticosteroids users compared to non users was 3.96 (Table 8-6).

6 Discussion

ON has been frequently described in cancer patients. Although ON in cancer patients has been usually considered to be caused by cancer treatment, malignancy itself has been also associated with ON in general reviews (Assouline-Dayan 2002, Bouquot 2000). Bouquot and McMahon (2000) listed cancer-induced hypercoagulation as a factor capable of compromising marrow blood flow thus increasing risk of ON.

In the GPRD study presented here, the estimated incidence rates of ON were 1.13 per 10,000 person-years (95% CI: 0.72-2.21) and 0.31 per 10,000 person-years (95%CI: 0.27-0.35), for the cancer cohort and general population, respectively. However, because underdiagnosis and misdiagnosis of ON in the past (Bouquot and McMahon 2000) the actual rate may be much higher than reported in the database. The list of codes used to identify patients with ON (Table 8-1) consisted of some rather aspecific terms (e.g., debridement). The review of computerized patients profiles of potential cases in the cancer cohort revealed that all identified patients fulfilled the case criterion. However, profiles of patients identified among the general population were not manually reviewed. Therefore, it cannot be excluded that the number of cases in the general population was overestimated and so was the incidence rate of ON. In such instance, the difference between ON incidence rates in the cancer cohort and general population would be even more striking.

Cancer treatment: chemotherapy with and without corticosteroids, and radiotherapy is well described risk factor for ON. Several chemotherapeutic agents, e.g., adriamycin, bleomycin, methotrexate, cyclophosphamide, 5-fluorouracil and cytarabine have been reported to cause this severe side effect (Harper 1984, Obrist 1978, Marymont 1986, Sung 2002, Schwartz 1982). In the GPRD study presented here, the risk of ON induced by chemotherapy was not evaluated. Details on chemotherapy are not registered in this outpatients database, thus not allowing such analysis in short time without contacting general practitioners.

Fourteen cases of ON were found among cancer patients in GPRD. None of them was recorded to be treated with bisphosphonates. However, it is likely that information regarding IV bisphosphonates use was not collected in this outpatients database. Therefore, no conclusions may be drawn from this data.

According to published evidence, systemic corticosteroid therapy is the main risk factor for non-traumatic ON. In our study, the risk of ON in systemic corticosteroids users was almost 4 times higher than in general population. However, data on other risk factors for ON which could be present in the corticosteroids cohort, e.g., anti-cancer treatment or diagnosis of SLE, were not collected. Therefore, the results can be confounded.

7 Conclusions

- Systemic corticosteroid therapy is a strong risk factor for ON.
- ON is a well documented complication of anti-cancer therapy. In GPRD in the United Kingdom, the incidence of ON in cancer population is over 4 times higher than in general population. However, since data on anti-cancer chemotherapeutic drugs and on IV bisphosphonates are not complete in this outpatients database, these risk factors cannot be assessed.
- The jaw bones, unique among skeletal structure because of the presence of the teeth, are frequently subject of local infections, which is considered to be an additional main risk factor for ON in this location. Other specific risk factors for the jaw ON are trauma and local anesthesia.

8 Tables

Table 8-1 READ, OXMIS and ICD 8 codes used for case identification

READ code	Diagnosis
J06y600	Osteoradionecrosis of jaw
N334900	Osteonecrosis due to drugs
N334C00	Osteonecrosis due to haemoglobinopathy
NyuC400	Other secondary osteonecrosis
NyuC500	Other osteonecrosis
NyuCC00	Osteonecrosis in other diseases classified elsewhere
N301.13	Sequestrum of bone
7K1C200	Sequestrectomy of bone
N334000	Avascular necrosis of bone, site unspecified
N334.00	Avascular necrosis of bone
N334100	Avascular necrosis of the head of humerus
N334200	Avascular necrosis of the head of femur
N334300	Avascular necrosis of the medial femoral condyle
N334311	Femoral condylar avascular necrosis
N334400	Avascular necrosis of the talus
N334500	Avascular necrosis of capitellum
N334600	Avascular necrosis of lateral femoral condyle
N334700	Avascular necrosis of other bone
N334800	Idiopathic aseptic necrosis of bone
N334z00	Avascular bone necrosis NOS

7K12B00	Debridement of bone
7K12D00	Arthroscopic debridement of patella
7K35400	Arthroscopic debridement of knee joint
OXMIS code	**Diagnosis**
7201NB	Bone necrosis
7239AF	Femur head avascular necrosis
7329AH	Avascular necrosis hip
9906ON	Osteoradionecrosis
K004E	Sequestrectomy skull
K7941A	Ankle sequestrectomy
K7941AA	Sequestrectomy bone
ICD 8 code	**Diagnosis**
7211	Aseptic necrosis of bone

Table 8-2 READ, OXMIS and ICD 8 codes for mandibulectomy and maxillectomy

READ code	Diagnosis
7J11.12	Mandibulectomy
7J11400	Total mandibulectomy
7J11500	Segmental mandibulectomy
7J16A00	Sagittal split mandibular osteotomy
7J16B00	Vertical sub-sigmoid mandibular osteotomy
7J10100	Total maxillectomy
7J10.12	Maxillectomy
7J10200	Partial maxillectomy
7J10300	Extended maxillectomy
OXMIS code	**Diagnosis**
K2582	Mandibulectomy
K2582AB	Mandibulectomy

Table 8-3 Incidence of ON in GPRD in the United Kingdom

	ON cases (N^o)	Person-yrs	Incidence Rate (x 10,000 person-yrs) (95% CI)
Cancer cohort	14	106,477	1.31 (0.72-2.21)
General population	278	8,998,314	0.31 (0.27-0.35)

Table 8-4 Incidence of ON by age-group among a cohort of cancer patients in GPRD

Age-group (yrs)	Person-yrs	ON cases (N^o)	Incidence Rate (x10,000 person-yrs)
20 -39	6,539	0	0
40 -59	29,135	4	1.37
60 -84	70,801	10	1.41
Total	106,475	14	1.13

Table 8-5 Incidence of ON by age-group among general population of patients in GPRD

Age-group (yrs)	Person-yrs	ON cases (N^o)	Incidence Rate (x10,000 person-yrs)
20 -39	3,268,001	62	0.19
40 -59	3,286,455	93	0.28
60 -84	2,443,855	123	0.50
Total	8,998,314	278	0.31

Table 8-6 Incidence rate and relative risk of ON in systemic corticosteroids users compared to the general population.

	Incidence Rate (x 10,000 person-yrs) (95% CI)	Relative Risk (95% CI)
Corticosteroids non users cohort*	0.25 (0.22-0.29)	1
Corticosteroids user cohort	0.99 (0.74- 1.31)	3.96 (2.60-5.39)
*General population cohort with systemic corticosteroids users excluded.		

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