Letters to the Editor

Jaw avascular bone necrosis associated with long-term use of biphosphonates

Bisphosphonates are currently used to prevent bone complications and to treat malignant hypercalcemia in patients with multiple myeloma, or bone metastases from breast and prostate cancers [1].

Within the last year we observed 10 patients who developed jaw bone necrosis while on treatment with zoledronic acid (Zometa®; Novartis) or pamidronate. All the patients had breast cancer with skeletal disease and received long-term treatment with bisphosphonates (range 14–48 months, median 30 months). Four patients developed this complication after tooth extraction or other odontostomatological procedures, and six had a spontaneous event. All patients but one had inferior mandibular necrosis.

Patients started to complain of jaw pain, difficulty in masticating and in brushing teeth. The clinical appearance simulated dental abscesses or osteomyelitis. Biopsy of the involved area showed the presence of necrotic lacunae, with infiltration of lymphocytes and histiocytes. In six cases, histological or cytological diagnosis of suspicious osteomyelitis was done (Figure 1).

This pathological feature, identified as 'jaw avascular bone necrosis', appears as a growing, painful, unilateral swelling of the jaw in patients receiving bisphosphonates [2–4]. Pain is frequently resistant to common anti-inflammatory drugs, causing severe impairment of quality of life. The definitive cure of avascular bone necrosis is controversial [4]. Surgical treatment and the use of hyperbaric oxygen seem to be partially effective. The removal of painful teeth may alleviate symptoms, but it eventually leads to further exposure of the bone [2]. In these cases discontinuation of bisphosphonates may be advocated, although the clinical benefit of this has not yet been proven.

In our experience, four patients underwent curettage of the affected mandible, but in two patients the symptoms persisted. Subsequently, one patient experienced a mandibular fistula, with persistence of pain and purulent secretion, despite massive use of antibiotics.

One patient with strong radiological suspicions of a jaw metastasis, was treated with local radiotherapy, but without clinical benefit. Afterwards, she developed a mandibular fistula. Another patient, after receiving hyperbaric oxygen therapy with no benefit, underwent wide resection of the affected bone, with no results. Another patient was treated with partial resection of the mandible, with a mild clinical improvement.

Pamidronate and zoledronate are nitrogen containing bisphosphonates and bind preferentially to sites of active bone resorption, exerting direct effects on osteoclastic activity through different mechanisms, including cytoskeleton changes, decreased liposomal function and inducing osteoclast apoptosis [1, 4, 5]. Normal osteoclast is vital to bone turnover, while its inhibition halts bone resorption, leading to the accumulation of non-vital osteocytes, microfractures of mineral matrix and bone necrosis. The selective appearance of this process in the jaw may be due to the specific anatomical pattern of harboring teeth, thus uniquely exposing this part of the skeleton directly to the open environment [2] and to continuous trauma due to mastication or to odontostomatological interventions.

The antiangiogenic effect attributed to bisphosphonates might play a role, together with microtrauma and inflammation, in causing ischemic changes [1, 4, 5].

Understanding the precise mechanisms involved in the process may lead to the prevention of this skeletal complication. Long-term routine use of drugs should take into account the risk of this relatively uncommon event.

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the user’s risk profile (hereditary, familial or personal) and expectations in requesting counselling. The oncologist defines the user’s educational/cultural level and their motivations and delay risk estimation. Communication modalities are geared to risk, thereby avoiding piecemeal data collection that would pathological files, to construct the pedigree and to estimate also obtains all the information necessary, including clinical-familial or hereditary cancer (T0). At this step, the counsellor wishes to know their cancer risk. Decisional empowerment when the user is fully empowered to decide whether he/she hereditary and familial tumours.

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Comment on ‘Cancer genetic counselling’ by P. Mandich et al. (Ann Oncol 2005; 16: 171)

With the advent of genetic tests, genetic counselling is attracting increasing attention, as also shown by the recent letter by Mandich et al. [1], which addressed some aspects of our oncologist-based multistep model of cancer genetic counselling [2]. Perhaps the features of our model can be appreciated if we explain the rationale that prompted it. The philosophy and practice of the model emerged from a clinical oncological setting [2]. It was specifically designed to meet the user’s needs of physical, mental and social well-being as recommended by the WHO [3], and is in keeping with the Italian National Health Plan in force when the model was designed, in that it empowers users to make an informed, fully aware choice among the various preventive, diagnostic and therapeutic options available [4]. The model, which employs an interdisciplinary team, identifies and manages at-risk subjects, and promotes the early diagnosis of invasive and preinvasive hereditary and familial tumours.

Pedigree construction and genetic testing (T1) occur only when the user is fully empowered to decide whether he/she wishes to know their cancer risk. Decisional empowerment derives from extensive information-giving about all aspects of familial or hereditary cancer (T0). At this step, the counsellor also obtains all the information necessary, including clinical-pathological files, to construct the pedigree and to estimate risk, thereby avoiding piecemeal data collection that would delay risk estimation. Communication modalities are geared to the user’s educational/cultural level and their motivations and expectations in requesting counselling. The oncologist defines the user’s risk profile (hereditary, familial or personal) and informs them of the possibility, limits and implications, also for their family, of risk estimation, and of prevention options so that the user can decide whether to proceed or not with counselling. At crucial steps of counselling, the psycho-oncologist evaluates also the user’s coping style, which is an indicator of psychological well being [5]. A grave cognitive deficit and a severe psychopathologic condition preclude continuation of counselling because fully aware consent (i.e. ‘empowerment’) and not just informed consent is required to proceed from step to step of the model. The counsellor verifies acquisition of information by questioning the user. The counsellor–user relationship is considered a partnership in which a dynamic feedback of information from and to the user is established. Gene testing is not appropriate for everyone [6]. Not all users have a genetic risk.

Given the high psychological impact of cancer, global counselling is particularly important and requires the specific professional figures in the field of hereditary and familial cancer. It is conceivable that, given their training and daily exposure to patients, oncologists are able to estimate personal risk, to propose diagnostic/therapeutic strategies and to explain these to the user considering their healthy or disease status.

The multistep counselling model, endorsed by the Italian National Health Service for application in patient care, is being used in some centers of the Network for Hereditary Breast and Ovarian Cancer. Information provided by the media or on educational websites, even when ‘officially’ sanctioned, needs to be ‘interpreted’ by the health professional according to each user’s needs.

In conclusion, our multistep model is not intended to replace classical genetic counselling, but rather to provide an alternative that fosters the oncologist–user partnership in order to promote early diagnosis and prevention.

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References