Avascular Osteonecrosis of the Jaw as a Side Effect of Bisphosphonate Treatment

Aristotle Bamias  Evangelos Terpos  Meletios A. Dimopoulos

Department of Clinical Therapeutics, University of Athens Medical School, Greece

Bisphosphonates are widely used for the treatment of bone disease in multiple myeloma and solid tumors. Side effects consist of pyrexia, renal function impairment, and hypocalcemia. Recently, a new complication has been described: avascular osteonecrosis of the jaw (ONJ). The risk of this complication is related to the type of bisphosphonate (it is higher with zoledronic acid compared to pamidronate) and the duration of therapy [1]. Up to now the major precipitating factor associated with its development is the history of recent dental procedures or trauma. This led to the endorsement of oral hygiene, avoidance of invasive dental procedures and assessment by experienced medical staff as guidelines for patients receiving bisphosphonates by various Dental and Medical Associations [2, 3].

The mechanisms underlying the development of this complication are not fully understood. Bisphosphonates can de-range repair and remodelling mechanisms which are mobilized by oral mucosa following mucosal injury and the resulting microbial insult. The continuous, very potent decrease in bone turnover caused by zoledronic acid may lead to increased bone fragility and, in combination with other local factors that are present in the jaw, to the development of ONJ. In addition, impaired blood supply has been implicated in the development of ONJ. There have been several reports indicating that zoledronic acid has anti-angiogenic activity [4, 5]. Thus, the inhibition of capillary angiogenesis may lead to the development of ONJ. It is reasonable to assume that the addition of an antiangiogenic factor will act synergistically to bisphosphonates in that respect. Both vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) have been suggested to play a role in the repair and remodelling of maxillofacial bone. Therefore, inhibition of these agents may, theoretically, contribute to the development of ONJ.

A number of case reports are supporting the notion that inhibition of angiogenic factors may be a precipitating factor of ONJ [6–8], although such reports in the context of the large phase III trials of these agents are lacking. These reports included patients treated with sunitinib, an inhibitor of the tyrosine kinases of VEGF, PDGF, c-kit, FLT3 and RET, or bevacidumab, a monoclonal antibody, which solely inhibits VEGF. Taken together these reports underline the importance of VEGF in the development of ONJ. The report of Bozas et al. [9] in this issue of ONKOLGIE adds to this information, since their patient was also treated with sunitinib.

There are two observations in this report, which are worth mentioning. The occurrence of ONJ was unexpectedly rapid: after the first infusion of zoledronic acid. This is in sharp contrast with the almost 2 years median time to the development of ONJ, reported in the literature. The patient had already been receiving sunitinib for 5 months, which suggests a synergistic effect between sunitinib and zoledronic acid. The other interesting observation is the fact that complete resolution of ONJ was achieved. Data from the literature suggest that healing is not usually achieved and the typical course of ONJ is that of remissions and relapses [1, 10]. Whether ONJ associated with anti-angiogenic factors is more easily reversible or the fact that the patient had received only one zoledronic acid infusion may have played a role in the successful management of this complication cannot be determined from the available data so far.

What is the significance of these reports and what are their therapeutic implications? First, the true magnitude of the problem is unknown. As shown in the case of bisphosphonates, prospective evaluation is necessary to accurately estimate the incidence of ONJ [1, 10]. Such information regarding anti-angiogenic agents are lacking. In the light of these reports should the concurrent administration of bisphosphonates and anti-angiogenic therapies be re-evaluated? Taking into consideration the extremely limited available data the answer is: no. Nevertheless, several relevant issues should be taken into account. Anti-angiogenic therapy represents an ef-
effect of treatment for several malignancies. These agents are not known to cause ONJ by themselves but they may rather augment this effect of bisphosphonates. The latter are also used in cases of bone metastases but they are not indicated for all patients with this manifestation. In most solid tumors they are indicated only for symptomatic disease. Therefore, it is essential that they are not used outside their indication because in this case many patients may be at increased risk of ONJ unnecessarily.

Until more data on ONJ associated with the use of anti-angiogenic agents is available, it is important that preventive measures, indicated by various medical and dental associations regarding the use of bisphosphonates, are rigorously implemented. These measures have been shown to significantly decrease the incidence of ONJ in multiple myeloma as well as breast cancer [11]. There is no reason to believe that they will not be effective in the context of anti-angiogenic therapy.

References


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