Reduction of osteonecrosis of the jaw (ONJ) after implementation of preventive measures in patients with multiple myeloma treated with zoledronic acid

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Background: Osteonecrosis of the jaw (ONJ) is a well-described complication of bisphosphonates use in patients with multiple myeloma (MM). We investigated whether the occurrence of ONJ decreased after the implementation of preventive measures in 128 patients with MM who received zoledronic acid.

Patients and methods: Patients with MM who received zoledronic acid were included in this analysis. Patients with a previous use of other bisphosphonates were excluded; patients were stratified into group A (n = 38) and group B (n = 90) if treatment was started before or after the implementation of preventive measures.

Results: One hundred and twenty-eight patients were included in this analysis. Sixteen patients (12.5%) developed ONJ—group A: 8 (26.3%), group B: 2 (6.7%) (P = 0.002). The incidence rate (IR) was 0.671/100 person-months for group A and 0.230/100 person-months for group B [IR ratio 2.92, P = 0.029, 95% confidence interval 1.06–8.03]. No patient in group B developed stage III ONJ.

Conclusion: In conclusion, the risk of developing ONJ after treatment of zoledronic acid is reduced (but not deleted) by the implementation of preventive measures.

Key words: multiple myeloma, osteonecrosis, preventive measures, zoledronic acid

introduction

Biphosphonates are used for the treatment of bone involvement by multiple myeloma (MM) and solid tumors [1, 2]. Side-effects consist of pyrexia, renal function impairment and hypocalcemia. Recently, a new complication has been described: avascular osteonecrosis of the jaw (ONJ) [3–7].

We and others have previously reported that the risk of ONJ is increased with time and use of zoledronic acid and dental work or trauma is usually the precipitating factor [8–13]. This led to the endorsement of oral hygiene, avoidance of dental procedures and assessment by experienced medical staff as guidelines for patients receiving bisphosphonate treatment by various Medical and Dental Associations and expert panels [14–20]. Nevertheless, the effect of the application of such measures has not been studied yet.

Since January 2003 all our patients treated with bisphosphonates have been entered into a database to prospectively evaluate the development of ONJ. Type of bisphosphonates, primary cancer, time of exposure, other therapies and development of ONJ were all recorded. For treatment before 2003, the medical records of all patients were reviewed and the above data were entered into the database retrospectively. At the same time, preventive measures were applied to our patients. More specifically, all patients were assessed by their dentist before the initiation of zoledronic acid to identify existing infections, ill-fitting dentures and compromised teeth that may eventually require intervention. All dental work-up that was necessary was done before the start of treatment with zoledronic acid. If major procedures like extraction were necessary, then the patient was referred to a specialized dental surgeon (IM). Whenever possible, the less invasive endodontic techniques with preservation of the dental root were preferred over total tooth extraction. Zoledronic acid was started 6–8 weeks after invasive dental procedures were carried out provided that complete healing was documented. All patients and their dentists were informed about the risk of ONJ and were advised not to proceed to any dental procedures without prior consultation with us. All patients were advised to maintain good oral hygiene.

The aim of the current study was to determine whether the application of such measures resulted in a reduction of the occurrence of ONJ in patients with MM treated with zoledronic acid.

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patients and methods

In this analysis, we included patients with MM who started treatment with bisphosphonates until 31 November 2006 and received at least six infusions. Patients were followed until April 1 2008. Only patients treated with zoledronic acid were included. Patients who initially received other bisphosphonates and were later switched to Zoledronic acid were excluded. ONJ was diagnosed by a maxillofacial surgeon (IM) on the basis of the following criteria: persistence of exposed bone in the oral cavity after adequate treatment for at least 6 weeks, associated with symptoms like pain and purulent discharge in the absence of focal myelomatous involvement and without previous radiotherapy to the affected area. Biopsy was carried out if exclusion of myelomatous involvement was clinically necessary. For treatment before 2003, medical records were reviewed in order to exclude symptoms and signs of ONJ; no patient with a high probability of ONJ was identified.

Zoledronic acid was administered at 4 mg over 15 min every 4 weeks indefinitely. There are no formal guidelines for use of bisphosphonates in Greece and in our institution we practice continuous use of these drugs. Administration of zoledronic acid was stopped in all patients who developed ONJ. In patients, with documented healing of ONJ and with evidence of active myeloma, we reintroduced zoledronic acid at a dose of 4 mg i.v. every 2–3 months.

statistical analysis

All analyses were carried out using the SPSS statistical software (SPSS for Windows, version 12.1, SPSS Inc., Chicago, IL) and STATA statistical software (STATA Corporation: Stata/SE 8.0 for Windows, College Station, TX). Patients were classified into two groups depending on the date of initiation of treatment in relation to the start of implementation of the preventive measures [Group A (before): 25/8/1998–31/12/2002, group B (after): 1/1/2003–31/11/2006]. The proportions of patients who developed ONJ between the two groups were compared with the Fisher’s exact test. For continuous variables, the Mann–Whitney tests were used for the comparisons of the means or the medians. Occurrence of ONJ was analyzed as row percentages as well as incidence rates (IRs) (number of new cases of osteonecrosis during follow-up/100 person-months). The incidence rate ratio (IRR) of developing ONJ in patients who belonged to group A compared with those in group B and its associated 95% confidence interval (CI) were also estimated with the score test. Survival analysis was used to estimate the hazard of developing osteonecrosis, with time of exposure to zoledronic acid being the primary time variable. Throughout the analysis, a level of 5% was used to denote statistical significance.

results

exposure to bisphosphonates and development of osteonecrosis

The earliest treatment with zoledronic acid was in August 1998. The characteristics of the 128 patients included in our analysis, according to the time of treatment initiation, are shown in Table 1. Thirty-eight patients were included in group A and 90 patients in group B. All patients routinely received pulse dexamethasone 40 mg for 4 days every 4 weeks as part of their treatment. There were no differences in the use of thalidomide or bortezomib between the two groups (Table 1).

As expected, median time of exposure to bisphosphonates was significantly longer in group A (40 versus 24.6 months, \( P < 0.001 \)). Sixteen patients (12.5%) developed ONJ; 10 in group A (26.3%) and six in group B (6.7%) (\( P = 0.002 \)). Median time of exposure to bisphosphonates was 32.5 months for patients with osteonecrosis (5.1–61), compared with 29 (3–103) for patients with no osteonecrosis (\( P = 0.285 \)). Time to ONJ was similar among patients of groups A and B (median time of exposure: 35 months versus 30.3 months, respectively, \( P = 0.118 \)). There was not any statistically significant association among the incidence of ONJ and the use of thalidomide or bortezomib.

Table 2 shows the IRs of ONJ in the two groups. There was a statistically significant, almost three-fold, reduction in the IR of osteonecrosis for patients of group B compared with patients of group A (IRR = 2.920, \( P = 0.0296 \)). The cumulative hazard for development of ONJ was 16% (95% CI 6% to 31%) for group A and 5.5% (95% CI 1% to 16%) for group B after 2 years of treatment.

characteristics and management of patients with ONJ

Seven men and nine women developed ONJ. No patient had received radiation at the area of the head and neck (Table 3).
At the time of ONJ diagnosis, 10 patients were in remission and six had refractory or relapsed myeloma. Eight patients in group A and four patients in group B had dental extraction within the last year preceding the diagnosis of ONJ. In one patient (group B), dental implants were placed few months before the diagnosis of myeloma and one patient had dentures (group A). In two patients, ONJ developed spontaneously without any preceding dental procedure (one in each group). In group B, three patients proceeded to dental extractions despite our advise. The mandible was involved in 13 patients, the maxilla in two cases and both sites in one patient. No stage III ONJ was diagnosed in patients of group B. Biopsy was obtained in five cases showing no involvement by myeloma. Treatment of ONJ was conservative consisting of antibiotics, local rinses and mouth washes and minimal surgery to eliminate the sharp edges that may cause trauma to surrounding soft tissues. In five patients (three in group A and two in group B), ONJ healed (defined as sustained absence of exposed bone and symptoms) and in one patient (group A) initially resolved but recurred 18 months later (Table 3). The remaining 10 patients had persistent disability with recurrences of purulent discharge and pain. The median follow-up after the development of ONJ was 10.2 months (range 2.5–55 months).

Zoledronic acid was reintroduced in two patients who had documented and sustained healing of ONJ and evidence of active myeloma. Among patients who discontinued zoledronic acid, one subsequently developed a skeletal event.

**discussion**

We found a significant, almost three-fold, decrease of zoledronic acid-related ONJ since we implemented preventive measures. During this period, the management of MM patients in our center has not changed: dexamethasone was administered to all patients using the same dose and schedule, thalidomide and bortezomib use did not differ between the two groups, while no patients received radiation to the area of head or neck. In our analysis, we elected to include only patients who received zoledronic acid, without prior exposure to pamidronate. The only relevant difference between the two groups was the time of exposure: expectedly, it was significantly longer for patients treated before 2003 and this is a weakness of our study. Since time of exposure is a crucial factor for the development of ONJ, it should be taken into account in the analysis and interpretation of the results. For this reason, we analyzed IRs, which take into account this factor, and we found a significant difference between the two groups. We, therefore, believe that the implementation of the preventive measures is the reason for the significant reduction of ONJ occurrence in our patients. A limitation of our study is that the diagnosis of ONJ before 2003 was retrospective. Thus, we cannot exclude that few cases of ONJ may have been missed. Nevertheless, this is unlikely since ONJ causes intense symptoms, which cannot remain unrecognized and our retrospective review of the medical records of the patients did not reveal any case with probable ONJ.

Zoledronic acid is valuable in the treatment of MM. Therefore, much effort is required in order to reduce the risk of developing ONJ and also improve the management of this complication. Current guidelines by the American Society of Clinical Oncology (ASCO) quote that due to the increased risk of ONJ with zoledronic acid ‘patients may prefer pamidronate to zoledronic acid until more data become available’. In addition, there is evidence that a three-monthly (instead of one-monthly) schedule of zoledronic acid

**Table 3.** Characteristics and outcome of patients who developed ONJ

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Gender</th>
<th>Myeloma status at ONJ diagnosis</th>
<th>Procedure before ONJ diagnosis</th>
<th>ONJ stage/outcome</th>
<th>Time of exposure to zoledronic acid (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>48</td>
<td>F</td>
<td>Remission</td>
<td>Extraction</td>
<td>Stage II/healed</td>
<td>38</td>
</tr>
<tr>
<td>2</td>
<td>63</td>
<td>F</td>
<td>Remission</td>
<td>Dentures</td>
<td>Stage II healing/relapse</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>75</td>
<td>F</td>
<td>Relapsed/refractory</td>
<td>Extraction</td>
<td>Stage II/nonhealed</td>
<td>30</td>
</tr>
<tr>
<td>4</td>
<td>63</td>
<td>F</td>
<td>Remission</td>
<td>Extraction</td>
<td>Stage II/healed</td>
<td>36</td>
</tr>
<tr>
<td>5</td>
<td>54</td>
<td>F</td>
<td>Remission</td>
<td>Extraction</td>
<td>Stage II/improvement</td>
<td>61</td>
</tr>
<tr>
<td>6</td>
<td>52</td>
<td>M</td>
<td>Remission</td>
<td>Extraction</td>
<td>Stage II/nonhealed</td>
<td>56</td>
</tr>
<tr>
<td>7</td>
<td>64</td>
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<td>Relapsed/refractory</td>
<td>Extraction</td>
<td>Stage III/nonhealed</td>
<td>25</td>
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<tr>
<td>8</td>
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<td>None</td>
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<td>34</td>
</tr>
<tr>
<td>9</td>
<td>70</td>
<td>F</td>
<td>Relapsed</td>
<td>Extraction</td>
<td>Stage III/nonhealed</td>
<td>53</td>
</tr>
<tr>
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<td>F</td>
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<td>Extraction</td>
<td>Stage II nonhealed</td>
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<tr>
<td>Group B</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>75</td>
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<td>Remission</td>
<td>None</td>
<td>Stage I/healing—reintroduction of zoledronic acid</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>66</td>
<td>F</td>
<td>Remission</td>
<td>Extraction</td>
<td>Stage II/nonhealed</td>
<td>33</td>
</tr>
<tr>
<td>3</td>
<td>68</td>
<td>M</td>
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<td>Extraction</td>
<td>Stage II/nonhealed</td>
<td>29</td>
</tr>
<tr>
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<td>Extraction</td>
<td>Stage II/improvement</td>
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<td>Extraction</td>
<td>Stage II/nonhealed</td>
<td>54</td>
</tr>
<tr>
<td>6</td>
<td>57</td>
<td>F</td>
<td>Remission</td>
<td>Implants</td>
<td>Stage II/healing—reintroduction of ZA</td>
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</tbody>
</table>

ONJ, osteonecrosis of the jaw; ZA, zoledronic acid.
administration results in reduction of ONJ [21]. In a recent report, prophylactic antibiotics before and during dental procedures may reduce the risk of developing ONJ [22]. Our study indicates that the measures already endorsed by Medical and Dental Associations, ASCO and Food and Drug Administration reduce this risk. Nevertheless, other mechanisms of developing ONJ apart from local trauma may exist and, therefore, research investigating the pathophysiology of this complication should continue. Finally, our more recent patients with ONJ were diagnosed after a lot more education and awareness and this resulted in the lack of cases with advanced stage III ONJ.

acknowledgements

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references