

References

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Response:

Increased mortality with FLA compared with ADE

We agree with Lane et al that the difference in overall survival between fludarabine and high-dose cytosine (FLA) and cytosine, daunorubicin, and etoposide (ADE) could be a chance effect. The hazard ratio, as reported in our paper, has a 95% confidence interval (CI) that ranges from 1.01 to 1.77. Thus, our result is compatible with there being no adverse impact of FLA on survival; on the other hand, it is also compatible with a 75% increase in mortality. Because of this uncertainty, we were cautious in our interpretation: in the abstract we concluded that “FLA may be inferior,”^{1(p4614)} whereas in the discussion we said that “we found no evidence that fludarabine with high-dose cytosine was a better treatment than the standard MRC schedule of ADE.”^{1(p4620)} We believe that the latter statement is justified since, based on our results, it seems unlikely that FLA is actually better than ADE.

With regard to deaths in complete remission (CR), the Kaplan-Meier estimates at 4 years are a bit misleading and make it appear as if the death rate is nearly 3 times greater in the FLA arm (34% versus 12%). This is because there was a small number of late events in the FLA arm (4 deaths beyond 1 year—with only a small number of patients at risk, each event adds 3%-4% to the Kaplan-Meier estimate), but none beyond 1 year in the ADE arm. In terms of crude death rate, 20% (17/83) of patients in the FLA arm died in CR compared with 12% (10/84) in the ADE arm. There is no clear explanation for this moderate, and nonsignificant, difference. More patients died following transplantation in the FLA arm than in the ADE arm (10 versus 5, with 36 versus 37 transplantations performed, respectively), though this difference is not significant ($P = .13$). Of the remaining 12 deaths in CR, the

majority was from infection as would be expected, but there was no excess with fludarabine (4 in each arm). None of the deaths in CR was related to second malignancy. Although there was no difference between the arms in relapses (83 FLA, 84 ADE), slightly more of the relapsing FLA patients have subsequently died (45 FLA, 39 ADE). Thus, a number of factors combine—3 more deaths without CR, 7 more in CR, 6 more after relapse—to give the cumulative excess of 14 deaths in the FLA arm, and the borderline significant adverse effect of FLA on survival compared with ADE, as reported in our paper.

Although we have not identified any clear reason for the apparent adverse impact of FLA on survival, and on the basis of the CI in our study (lower limit of hazard ratio CI = 1.01), it may not actually be any worse than ADE; it could, however, be a lot worse (upper limit of CI = 1.77), so it would be reasonable on the current evidence to avoid using FLA routinely.

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To the editor:

Osteonecrosis of the jaws in newly diagnosed multiple myeloma patients treated with zoledronic acid and thalidomide-dexamethasone

In recent years, an increasing number of reports have pointed out the association between osteonecrosis of the jaws (ONJ) and the use of bisphosphonates as therapy of neoplastic bone disease or benign osteoporosis.^{1,2} The pathogenesis of this complication is unknown, although bisphosphonate-induced impaired bone resorption is likely to play a crucial role. Moreover, the relative contribution of microtrauma from chewing, repeated dental procedures, poor oral hygiene, cancer bone involvement, and concomitant chemotherapy has not been clarified yet.

In an attempt to identify the incidence of ONJ in a large, homogeneous series of patients with newly diagnosed multiple myeloma (MM) and to define the possible pathogenetic role of concurrent antimyeloma therapy, we retrospectively reviewed a series of 259 consecutive patients with symptomatic MM who were enrolled in the Bologna 2002 clinical

trial.³ By study design, all patients received 4 months of primary therapy with thalidomide (200 mg/d) combined with high-dose dexamethasone (40 mg/d on days 1-4, 9-12, and 17-20 on odd cycles and on days 1-4 on even cycles) followed by double autologous transplantation with 200 mg melphalan/m². Daily thalidomide (200 mg/d) and monthly courses of dexamethasone were continued until the second autologous transplantation. Intravenous zoledronic acid 4 mg every 28 days was administered throughout the whole treatment period and continued thereafter, at physician's discretion. Only patients receiving zoledronic acid for longer than 4 months were included in the present analysis.

Overall, 9 patients (3.47%) presented with suspicious findings of ONJ, which was subsequently confirmed at oral/maxillofacial diagnostic workup. As previously reported,⁴⁻⁶ the duration of exposure to bisphosphonates was closely related to an increased

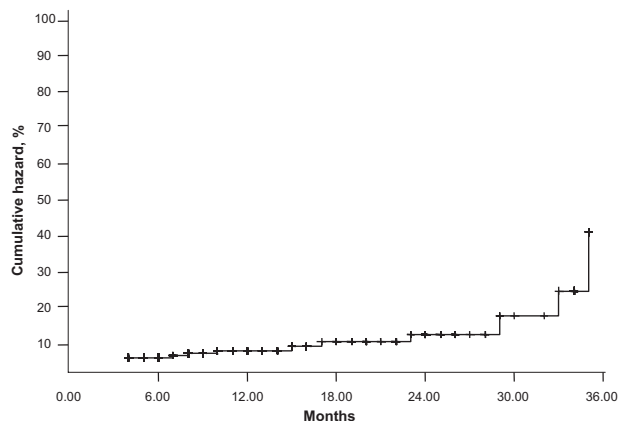


Figure 1. Cumulative risk of developing ONJ according to time of exposure to zoledronic acid.

incidence of ONJ; median duration of zoledronic acid therapy (10 months; range, 4-35 months, in the whole patient population) was significantly longer among patients experiencing ONJ compared with patients who did not show this complication (17 versus 10 months, respectively; $P < .01$) (Figure 1). ONJ occurred in the mandible in 6 cases (66.6%); symptoms of pain, swelling, or purulent discharge were present in all but one patient who was diagnosed as having exposed bone at routine dentistry examination. Four patients had a complete response to minimally invasive treatment and 3 patients showed a partial improvement, while no improvement was observed in the last 2 patients in whom a monoclonal plasma cell infiltrate of the mandible was detected.

Although patients' follow-up was shorter than in other studies, possibly accounting for the lower incidence of ONJ compared with that reported by others,^{4,6} the rate of ONJ after 24 months of zoledronic acid exposure was 6.6%, a value comparable with those found in other analyses.^{5,7} This observation might suggest that neither antiangiogenic activity of thalidomide, nor impaired bone remodeling related to dexamethasone, nor severe immunosuppression induced by high-dose melphalan was an important additional risk factor for the development of ONJ. Bisphosphonates represent the standard of care for treatment and prevention of MM-related bone disease⁸; however, both physicians and patients should be aware of ONJ as a possible complication, and more attention should be paid to preventive measures.^{9,10}

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To the editor:

Use of the International System for Human Cytogenetic Nomenclature (ISCN)

One of the aims of the International System for Human Cytogenetic Nomenclature (ISCN)¹ is to prevent confusion in reporting research cytogenetics results. In this context, Massey et al² apparently overlooked the ISCN recommendations and their cytogenetic results were reported out of the proper form.

In concrete, the authors omitted the use of commas and slant lines in the description of karyotypes in Table 6 (footnotes) and Table 7. Moreover, the order of chromosome abnormalities in some karyotypes is not correct. There are also some mistakes in Table 7: sex chromosomes in patient 1 are described as XX and XY; because case 6 corresponds to a mosaic, the +21 has to be marked as a constitutional abnormality as exemplified by Hu et

al³; patient 7 has an i(7)(q10), which should be indicated as i(7)(q10), not as "isochromosome 7(q10)"; the description in patient 9 of the der(7) as originated from a t(1;17), probably means der(7) from a t(1;7) because chromosome 7 has q36 band but chromosome 17 has not; also in this patient the single colon is misused.

There are other errors in Table 6 (footnotes): the total of individuals is 43 not 42; one karyotype from the 7 boys is missing; the described karyotype "47XYder(14;21)(q10;q10)+21c" means that the der(14;21) is an acquired abnormality in a trisomic 21 clone, but in patient 9 (Table 7), who is the same case, the der(14;21) is described as a constitutional abnormality; moreover,