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Assessment of the impact of new UK guidelines on the management of aromatase inhibitor-associated bone loss

Sir, The aromatase inhibitors (AIs) anastrozole, letrozole and exemestane are approved for the adjuvant treatment of post-menopausal early breast cancer [1]. AIs suppress the non-glandular conversion of androgens to oestrogens and significantly reduce the levels of post-menopausal oestrogen [2]. Concerns about the possible adverse effects of lower oestrogen levels on post-menopausal bone health have been supported by the results of clinical trials for all three drugs [3]. There is general consensus that post-menopausal women commenced on AIs should be screened for osteoporosis by dual energy X-ray absorptiometry (DXA) [4] and such practice has been supported by guidelines produced by the American Society of Clinical Oncology (ASCO) [5]. Oral bisphosphonate therapy is thereby recommended for patients on an aromatase inhibitor with a history of hip/spine fragility fracture or a DXA T-score of ≤−2.5. A United Kingdom Expert Group (UKEG) has recently produced alternative guidelines supported by the National Cancer Research Institute Breast Cancer Study group and the National Osteoporosis Society on the evaluation, monitoring and treatment of bone loss in early breast cancer [6]. The UKEG guidelines recommend bisphosphonate therapy for patients on an AI (i) with treatment-induced premature menopause and either a history of vertebral/hip fragility fracture or a T-score <−1.0, (ii) ≥75 yrs old and ≥1 clinical risk factor for fracture and (iii) with a T-score of <−2.0 for any patient. All patients who are clinically deficient should receive calcium and vitamin D.

We estimated what the impact of the UKEG guidelines would have been using data from a cohort of 272 patients on aromatase inhibitors referred for DXA scanning to the Royal Lancaster Infirmary between March 2006 and September 2007, before these guidelines were published. This cohort represents 6.1% (272/4479) of all referrals during this period from a catchment population of 320,000. The mean age of the cohort was 66.3 yrs (s.d. 6.8 yrs). Data on duration of AI therapy were available in 82 patients. Of these, 43 (52.4%) had been on an AI for ≤6 months. The median duration of AI treatment was 6 months (interquartile range 1–12 months). Out of 204 patients, 69 (33.8%) had received prior tamoxifen. Out of 272 patients, 31 (11.2%) had a known fragility fracture, 10 (3.7%) were on a bisphosphonate, 60 (22.1%) were on tamoxifen and 161 (58.9%) were untreated.

Table 1 shows the impact of applying the UKEG guidelines. Using the UKEG guidelines, 84 (30.9%) of patients met the criteria requiring treatment in whom bisphosphonate treatment would have been advised. By applying these guidelines, we estimated that 40 (14.7%) and 84 (30.9%) of patients met the criteria requiring treatment in the ASCO and UKEG guidelines, respectively (Table 1). The application of UKEG guidelines would result in 44 additional patients or a 110% increase in the number of patients on AIs in whom bisphosphonate treatment would have been advised. This finding is most marked in patients over 75 yrs old.

We conclude that implementation of the UKEG guidelines will have a significant impact on the workload of bone density units and also the clinical management of patients on AIs which purchasers, osteoporosis and oncology specialists should be aware of and make provision for.

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>ASCO (%)</th>
<th>UKEG (%)</th>
<th>Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;45 (n=5)</td>
<td>0 (0)</td>
<td>2 (40)</td>
<td>-</td>
</tr>
<tr>
<td>45–74 (n=212)</td>
<td>26 (12.3)</td>
<td>47 (22.2)</td>
<td>+80.8%</td>
</tr>
<tr>
<td>≥75 (n=55)</td>
<td>14 (25.4)</td>
<td>35 (63.6)</td>
<td>+150%</td>
</tr>
<tr>
<td>Any age (n=272)</td>
<td>40 (14.7)</td>
<td>84 (30.9)</td>
<td>+110%</td>
</tr>
</tbody>
</table>

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Keywords

- New UK guidelines will have a major impact on the management of aromatase inhibitor bone loss.
Severe acute thrombotic exacerbation in two cases with anti-phospholipid syndrome after retreatment with rituximab in phase I/II clinical trial for refractory systemic lupus erythematosus

Sir, Rituximab is a chimeric mouse human monoclonal antibody against CD20 on B cells that has been approved for treatment for non-Hodgkin’s lymphoma and RA in the US/EU; its safety and efficacy in SLE has been reported previously [1, 2]. We report herein two cases of SLE, with APS, who developed severe flare after re-treatment with rituximab.

Summarized clinical courses are shown in Fig. 1. Case 1 was a 24-yr-old female with a 9-yr history of thrombocytopenia, who had been treated with corticosteroids, immunosuppressants, intravenous immunoglobulin and platelet transfusion. Two years prior, thrombocytopenia, fever, erythema and polyarthritis were gradually progressing and the first rituximab treatment regimen—two infusions of 1000 mg separated by 14 days—was applied in a Japanese Phase I/II clinical trial in SLE [3]. Rituximab effectively depleted B cells and a significant improvement of clinical manifestations observed; however, a pharmacokinetic examination found early clearance of rituximab due to human anti-chimeric antibody (HACA). The serum level of rituximab became undetectable 5 weeks after the second infusion with quantifiable HACA (287 ng/ml). Rituximab usually remains detectable for as long as 4–6 months post-treatment. Sixteen months after the first rituximab therapy, lacunar infarctions associated with APS appeared and SLE activity also began to increase, for which a second course of rituximab treatment was initiated. The first infusion was well tolerated, but a severe infusion reaction with rash and dyspnea occurred at the time of the second infusion. A modest level of HACA was detectable just before the first infusion (37.6 ng/ml), but this increased markedly (71 700 ng/ml) 3 weeks after the second infusion; however, an attempted rituximab administration completed with concomitant intravenous corticosteroid rescue. A third course of rituximab therapy was administered 7 months after the second course, but severe infusion reactions developed both at the first and second infusions, and a temporal stop/resume of rituximab infusion, repeated several times, with intravenous steroid rescue was performed. The serum level of HACA was 295 ng/ml before the first rituximab infusion and 324 ng/ml 3 weeks after the second infusion, with no detectable rituximab suggesting complete neutralization by HACA. One week after completion of this third regimen, high fever and headache emerged and a diagnosis of acute meningitis was made from an examination of cerebrospinal fluid. Paraplegia of the legs with pain suddenly developed, and an MRI confirmed transverse myelitis, which is known to be a clinical manifestation associated with APS as well as with...