Reviewer's report

Title: Skeletal metastasis diagnosed without bone pain showed fewer skeletal related events and death than those with bone pain in post-operative breast cancer patients

Version: 1 Date: 5 March 2010

Reviewer: francesco bertoldo

Reviewer's report:

MAJOR COMPULSORY REVISION

1. One of the most relevant bias in the paper is in the definition of SRE. Commonly (in RCT) SRE includes fracture, hypercalcemia, radiotherapy, spinal cord compression, orthopaedic surgery. The authors included in SRE also the use of morphine for pain. Furthermore it is not clear if radiotherapy for bone was for analgesia. Because the risk of SRE increases twofold after the first SRE (Hortobagy GN J Clin Oncol 1998) (Major PP Am J Clin Oncol 2005) it is not surprising that in patients with pain the use of morphine and radiotherapy (often used for analgesia) were more frequent than in patient without pain. Patients with these two “SREs” account for about the 66% in the pain group. The inclusion of morphine use and radiotherapy for pain in SRE classification resulted in an overestimation of the incidence of SRE in this group.

2. More details should be given about the characteristics of bone metastases at the diagnosis for the patients of both groups (type: lytic, blastic or mixed, site: axial or appendicular), since both type and site in the skeleton influence the incidence of SRE and prognosis.

3. Since the use of bisphosphonates significantly influences the risk of SRE (and pain) and considered that bisphosphonates show relevant differences in their efficacy, particularly between pamidronate and zoledronate, detailed informations about the type of BP, schedule and treatment duration, need to be given. The use of bisphosphonates (as other adjuvant therapies) should be considered in Cox’proportional hazard multivariate analysis.

4. Taking into account the prevalence of hypovitaminosis D in Japan and the necessity for good levels of vitamin D in BPs treated patients, data on vitamin D supplementation are needed; furthermore considering the effects of vitamin D deficiency on bone turnover and consequently on the risk of SRE.

5. The two groups of patients were stratified by the presence of pain, but there were described neither the criteria of pain diagnosis or the methods or scale to quantify it.

6. The intensive follow up adopted in the study after surgery, especially for what concern the frequent execution of total body scanning for detecting bone
metastases is not actually suggested by the International Guidelines. Authors have to discuss this point and the obtained Ethical Comitee approval and informed consensus by patients should be reported.

7 The limitations of the study are not be stated

8. Published data show that stratifying patients by pain (with or without) at the diagnosis of bone metastases there are not differences between the incidence of SRE in the two groups (Eastham J and coll (ASCO meeting 2005, abst 4561). These data should be discussed.

9. The median time from diagnosis of bone metastases to the first SRE in both groups should be reported in the results.

DISCRETIONARY REVISION
1. The discussion should try to explain the possible causes supporting the differences between the two groups (pain and no pain).

MINOR ESSENTIAL REVISION
1. Bibliography should be updated
2. Legends of tables are lacking.

Level of interest: An article of limited interest

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that i have not competing interests