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Original article

IAEA randomised trial of optimal single dose radiotherapy in the treatment of painful bone metastases

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ABSTRACT

Background: To determine the optimal single-dose radiotherapy schedule for pain from bone metastases in a multi-centre, international, randomised trial.
Patients and methods: 651 patients were randomised to either 8 Gy (n = 325) or 4 Gy (n = 326) radiotherapy. Pain at 4, 8, 12, 24 and 52 weeks was assessed using a Categorical Scale (CS) and a Visual Analogue Scale (VAS). The primary endpoint was response at 4 weeks.
Results: There was no significant difference in patient demographics and other co-variates. The complete response (CR) rate and ORR (complete or partial response) for all follow-up times were higher after 8 Gy (p = 0.02). The Kaplan–Meier actuarial rate (categorical scale) at 4 weeks for ORR was 80% after 8 Gy compared to 68% after 4 Gy (p = 0.0015). 117 re-treatments were given of which 72 were in the 4 Gy group and 45 in 8 Gy arm (p = 0.01).
Conclusions: There was a marked consistent difference in pain relief at all time points in favour of 8 Gy. These data reinforce the case for single dose 8 Gy radiotherapy to be recommended for metastatic bone pain in all healthcare settings.
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Bone metastases arise in up to 70% of all cancer patients and represent a major workload and cause of morbidity in cancer patients [1,2].

The pathogenesis of metastatic bone pain remains unclear [3,4]. Treatment of painful bone metastasis includes analgesics and adjuvant analgesics, bisphosphonates, surgery and nerve blocks, alongside anti-tumour therapy using endocrine therapy, chemotherapy, radiopharmaceuticals and beam radiotherapy (RT) [5]. RT is the mainstay of treatment for painful bone metastasis [6] accounting ~20% of the daily workload [7,8]. The mechanism of pain relief after RT is uncertain. Although the destruction of tumour cells followed by bone remodelling occurs, the rapid speed of onset and the maintenance of pain relief post-RT and absence of a dose response suggest that tumour cell kill is not the only factor. Other possible mechanisms include an effect on sensitive host cells producing pain mediators, direct effect on osteoclast activity, or disturbance of the neuronal transmission of pain. There is also likely to be a placebo effect [5].

Single dose treatments (8–10 Gy) are as effective as multifraction regimens (20–30 Gy in 5 to 10 daily treatments) and class 1 evidence comes from randomized trials and meta-analyses [9,10]. The optimal single dose of RT required for pain relief is unknown. Two studies have shown that 8 Gy yields better pain relief than 4 Gy, however, 4 Gy was effective in a large proportion of patients [11,12]. With 8 Gy overall response rates of 70–85% were observed compared to 43–59% after a single fraction of 4 Gy.

This IAEA sponsored multi-centre, international, randomised trial was undertaken to further explore the optimal single radiation dose for metastatic bone pain in a range of healthcare settings.

Patients and methods

Patients aged 18 years or more, with a histological diagnosis of malignancy, radiological evidence of painful bone metastasis and a life expectancy of 12 weeks or more were eligible for randomisation into the study. For patients with two sites of pain requiring

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separate treatment the same randomized treatment option was used for both sites, but response at each site was scored and analysed separately.

Institutional board review and informed consent in keeping with local and national regulatory practice was mandatory. Exclusion criteria were primary histology myeloma, bone metastasis in sites previously irradiated, previous radioisotope treatment, conditions or circumstances that may impede treatment or follow-up, and patients with complicated bone metastasis (pathological fractures, metastatic spinal cord compression).

At baseline all patients underwent a physical examination (including neurological examination), full blood count and biochemical screen, required within 7 days of randomisation. Randomisation was by fax of a registration form to the Central Trials Office confirming entry criteria returned within 24 h.

Patients were stratified according to single versus multiple bone metastasis, histology, and participating centre and randomised 1:1 to one of the following groups:

Group A: patients with a single site of bone pain to be treated.
Group B: patients with multiple sites of bone pain.

The randomization in group A was between a single dose of 8 Gy and a single dose of 4 Gy and in group B between a single dose of 8 Gy and 12 Gy in 4 fractions of 3 Gy given in 2 consecutive days with a minimum interfraction interval of 6 h.

Radiotherapy was delivered with megavoltage equipment with minimum nominal energy of 1.25 MeV. Single, direct (posterior) fields or parallel opposed fields technique was used to treat spinal metastasis, direct field or tangential fields for rib metastasis and two parallel opposed fields to treat pelvis, hip or long bones. The prescribed dose was to the 100% isodose with single fields, the central (mid-plane) dose for opposed fields and at depth for vertebrae defined at the centre of the vertebral body or 5 cm depth if this was not measured.

The treatment field encompassed a 2 cm margin on each side of the bone metastasis. For the spine fields at least one vertebra above and below the affected vertebrae were included. Any soft tissue extension of tumour was covered by a 2 cm margin.

All patients were simulated before irradiation. Verification (portal) films on the treatment machine were optional.

Re-treatment with 8 Gy was given to the initially treated site if moderate or severe pain persisted or recurred at 4 weeks or more after initial radiotherapy. A second re-treatment ($\geqslant$4 weeks after first re-treatment) could be given using the same criteria as first re-treatment.

Analgesic use was scored at baseline and at each follow up.

Endpoints and statistical analysis

The primary endpoint was the difference in the proportion of responders at 4 weeks from randomization. The study was powered to detect a 10% lower response rate in the experimental arms of each group with a two-sided p test where $\alpha = 0.05$ and $1 - \beta = 0.8$. Allowing for an attrition rate of 10%, a target sample size of 320 patients was defined for each arm, totalling 1280 patients.

A four-point categorical scale (CS) – none, mild, moderate or severe – and a 10 cm visual analogue scale (VAS) were used to measure pain. Patients were assessed at randomisation (baseline), at four, eight, twelve, twenty-four and fifty-two weeks after randomisation. A complete response (CR) was defined by no pain on the CS and a score of zero on VAS and partial response (PR) by an improvement by at least one category of pain (e.g. from moderate to mild) or a reduction in the VAS score of at least 10 mm. No response (NR) was defined by no change in pain category or a change of <10 mm on the VAS. Pain relief was also scored incorporating analgesic requirements to provide "combined pain relief" using a categorical scale (0 = none; 1 = non-opiates; 2 = weak opiates; 3 = strong opiates). CR was defined as total absence of pain; PR was an improvement by at least one pain category with either no analgesics or decreased or stable analgesics. Progression of pain was defined as an increase in the pain score by at least one category with analgesics either stable or increased or stable pain score with analgesics increased.

Statistical comparisons were carried out using JMP™, SAS Institute, Cary, NC, USA. Differences in patients' baseline demographics and treatment features were compared using χ^2 and Kruskal–Wallis tests for categorical and continuous covariates, respectively. Analyses were performed as per protocol with time to event calculated from day of randomisation. Response rates (RR) were calculated by dividing the number of patients who responded at a defined time point by the total population in the study (prevalence). A "best case" actuarial response rate was calculated using the Kaplan–Meier method and differences compared with the Mantel-Cox log-rank test. Prevalence was calculated using the actual number of patients seen at the particular follow-up and a χ^2 test used to compare differences between dose groups. Where appropriate, the defined level of significance was adjusted using Bonferroni's correction method for multiple comparisons.

Results

Between 22 January 2008 and 31 August 2012, 655 patients were randomised into Group A: 326 into Arm 1 and 325 into Arm 2 (see Consort diagram Fig. 1). Accrual into Group B (arms 3 and 4) of the trial was poor and only 40 patients were entered into Arm 3 and 30 to Arm 4 at the time of study closure. Therefore, only results for Group A have been analysed and are presented here.

Table 1 summarises the site treated and the primary tumours; these are well balanced. Table 2 gives demographic features and other co-variates.

Crude incidence (all follow-ups) and prevalence of pain relief at 4 weeks (primary endpoint) are shown in Table 3. Using the CS, there was a small but significant difference in favour of 8 Gy in the global comparison for all follow-up times and the number of complete responders was higher for those treated with 8 Gy compared to 4 Gy, although significant only at 8 weeks ($p = 0.03$). The ORR (overall response rate) was significantly higher for the 8 Gy dose group at the two time points shown in Table 3 and maintained at 8 and 52 weeks ($p = 0.03$). Using the VAS method rather than the CS, there is a reduction in the number of complete responders in both dose groups, but overall incidence and 4-week prevalence remain significantly higher after 8 Gy.

The actuarial rate (CS) at 4 weeks, calculated using the Kaplan–Meier method, showed a significant difference in ORR of 80% after 8 Gy compared to 68% after 4 Gy ($p = 0.0015$) but no difference in CR (32% *vs* 34%).

Combined pain relief is shown in Table 4. The difference between dose groups was highly significant if a global comparison was made for all follow-up times. Prevalence of complete responders at 4 weeks using the CS was significantly higher for patients treated with 8 Gy and this was maintained between 8 weeks and 52 weeks, although significant only at 8 weeks ($p = 0.0005$). The proportion of partial responders was similar at all follow-up times. The VAS method detected a significant difference in favour of 8 Gy only for complete responders assessed 4 weeks after randomisation.

A total of 117 retreatments were given; 72 after 4 Gy and 45 after 8 Gy ($p = 0.01$).

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