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Clinical Investigation

Dexamethasone for the Prevention of a Pain Flare After Palliative Radiation Therapy for Painful Bone Metastases: The Multicenter Double-Blind Placebo-Controlled 3-Armed Randomized Dutch DEXA Study

Yvette M. van der Linden, MD, PhD,[*,†] Paulien G. Westhoff, MD, PhD,[‡,§] Rebecca K. Stellato, PhD,[‖] Angela van Baardwijk, MD, PhD,[¶] Kim de Vries, MD,[#,] Francisca Ong, MD, PhD,[††] Ruud Wiggenraad, MD, PhD,[‡‡] Bonnie Bakri, MD,[§§] Gerda Wester, MD,[‖‖] Ilse de Pree, MD,[**] Lieneke van Veelen, MD, PhD,[¶¶] Tom Budiharto, MD,[##] Maaike Schippers, MD,[***] Anna K.L. Reyners, MD, PhD,[†††] and Alexander de Graeff, MD, PhD[‡‡‡]**

***Department of Radiotherapy, Leiden University Medical Centre, Leiden, the Netherlands; [†]Centre of Expertise in Palliative Care, Leiden University Medical Centre, Leiden, the Netherlands; [‡]Department of Radiotherapy, University Medical Centre Utrecht, Utrecht, the Netherlands; [§]Department of Radiotherapy, Radboud University Medical Centre, Nijmegen, the Netherlands; [‖]Department of Biostatistics, Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht, the Netherlands; [¶]MAASTRO, Maastricht, the Netherlands; [#]Department of Radiotherapy, National Cancer Institute, Amsterdam, the Netherlands; [**]Department of Radiotherapy, Erasmus Medical Centre, Rotterdam, the Netherlands; [††]Department of Radiotherapy, Medical Spectrum Twente, Enschede, the Netherlands; [‡‡]Department of Radiotherapy, Haaglanden Medical Centre, The Hague, the Netherlands; [§§]Department of Radiotherapy, Reinier de Graaf Hospital, Delft, the Netherlands; [‖‖]Radiotherapy Group Arnhem, Arnhem, the Netherlands; [¶¶]ZRTI, Vlissingen, the Netherlands; [##]Department of Radiotherapy, Catharina Hospital, Eindhoven, the Netherlands; [***]Bernard Verbeeten Institute, Tilburg, the Netherlands; [†††]Department of Medical Oncology, University of Groningen, University Medical Centre Groningen, Groningen, the Netherlands; and [‡‡‡]Department of Medical Oncology, University Medical Centre Utrecht, Utrecht, the Netherlands**

Corresponding author: Yvette M. van der Linden, MD, PhD; E-mail: ymvanderlinden@lumc.nl

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Purpose: After radiation therapy for painful bone metastases, up to 44% of patients report a pain flare (PF). Our study compared 2 dose schedules of dexamethasone versus placebo to prevent PF.
Methods and Materials: This double-blind, randomized, placebo-controlled trial allocated patients with painful bone metastases from solid tumors randomly to receive 8 mg dexamethasone before radiation therapy followed by 3 daily doses (group A), 8 mg dexamethasone followed by 3 doses of placebo (group B), or 4 doses of placebo (group C). Patients reported worst pain scores, study medication side effects, and opioid intake before treatment and thereafter daily for 14 days and on day 28. PF was defined as at least a 2-point increase on a 0 to 10 pain scale with no decrease in opioid intake or a 25% or greater increase in opioid intake with no decrease in pain score, followed by a return to baseline or lower. The primary analysis was by intention to treat with patients who had missing data classified as having a PF.
Results: From January 2012 to April 2016, 295 patients were randomized. PF incidence was 38% for group A, 27% for group B, and 39% for group C ($P = .07$). Although patients in group B had the lowest PF incidence, a relatively high percentage did not return to baseline pain levels, indicating pain progression. The mean duration of PF was 2.1 days for group A, 4.5 days for group B, and 3.3 days for group C ($P = .0567$). Dexamethasone postponed PF occurrence; in group A 52% occurred on days 2 to 5 versus 73% in group B and 99% in group C ($P = .02$). Patients in group A reported lower mean pain scores on days 2 to 5 than those in group B or C ($P < .001$). Side effects were similar.
Conclusions: There was insufficient evidence that dexamethasone reduced the incidence of radiation-induced PF. However, dexamethasone postponed the occurrence of PF and led to lower mean pain scores on days 2 to 5.

Introduction

For patients with advanced cancer and painful bone metastases, radiation therapy is an effective palliative treatment, with about 62% responding within 3 to 4 weeks after treatment.[1] No differences in pain response have been found between either a single fraction of 8 Gy or multiple fractions with higher total doses. Some patients experience a transient increase of pain shortly after radiation therapy, the so-called pain flare (PF), which has considerable detrimental effects on quality of life.[2] A recent review of prospective studies reported PF percentages ranging from 2% to 44%.[3]

Administration of anti-inflammatory drugs such as dexamethasone might have a direct beneficial analgesic effect on pain and prevent the occurrence of PF. In 2015, the Canadian NCIC SC 23 study in 298 patients showed that 5 daily 8-mg doses of dexamethasone significantly reduced the incidence of PF after a single fraction of 8 Gy from 35% to 26% ($P = .05$).[4] In The Netherlands, we performed a similar randomized study, the Dutch DEXA study, investigating the effectiveness and toxicity of 2 dose schedules of dexamethasone to prevent the incidence of PF after short schedule radiation therapy (1 × 8 Gy or 20-24 Gy in 5-6 fractions) for painful bone metastases, compared with placebo.

Methods and Materials

Study design

Our study was a randomized, double-blind, placebo-controlled, 3-armed trial in which patients were entered from 12 of the 21 Dutch radiation therapy institutes.[5] Eligible patients were aged 18 years or older, with uncomplicated painful bone metastases (ie, no actual or impending fracture and no neurologic symptoms caused by nerve root or spinal cord compression) from solid tumors. Pain intensity was between 2 and 8 on a numeric rating scale from 0 to 10, with no immediately expected changes in the analgesic regimen, as determined by the treating physician. Patients could be scheduled for 1 × 8 Gy or 20 to 24 Gy in 5 to 6 fractions. Patients were excluded when multiple painful bony sites were to be irradiated, the same bony site was treated before with radiation therapy, the patients were currently or recently (<1 week before randomization) using steroids or expected to use steroids within 2 weeks after start of radiation therapy, they had a life expectancy <8 weeks, or they had a Karnofsky Performance Status Scale score of ≤40. All participating centers received approval from local medical ethics boards, and written informed consent was obtained from all participating patients. This study is registered with ClinicalTrials.gov, number NCT01669499.

Randomization

Patients were randomly assigned (1:1:1) to receive orally 4 × 8 mg dexamethasone (group A), one 8-mg dose of dexamethasone followed by 3× placebo (group B), or 4× placebo (group C). Randomization was performed centrally using a computer-made randomization list and was stratified by radiation therapy schedule (single or multiple fractions) and by participating center. The outcome of the randomization was blinded for the treating radiation oncologist, patient, principal investigators, and study statistician.

Procedures

The study medication was manufactured and supplied centrally by the Department of Pharmacy of the University Medical Center Utrecht. The medication was provided in numbered medication boxes containing 4 identical capsules. Patients were instructed to take the first capsule at least 1 hour before the start of radiation therapy (day 0) and then every day for 3 days (days 1-3), preferably with breakfast. Treatment of any pain after radiation therapy was at the discretion of the treating physician. In patients with severe pain not responding to analgesic increase, treatment with open-label dexamethasone was allowed.

Patients were given a diary to report pain and quality of life and instructed to describe pain experienced at the irradiated bony localization only. For pain, the brief pain inventory was used with pain scores ranging from 0 (no pain) to 10 (worst imaginable pain).[6] Patients reported their worst daily pain score at baseline before radiation therapy (day 0) and then once daily for 14 days (days 1-14) and on day 28. They also recorded their daily pain medication intake. Furthermore, they answered 2 additional questions on restlessness and appetite to investigate possible side effects of the study medication, scored from 1 (not at all) to 4 (very much). For quality of life, patients completed the EORTC QLQ-C15-PAL questionnaire and the EORTC QLQ-BM22 bone metastases module at baseline (day 0) and on days 7, 14, and 28.[7,8]

Outcomes

The primary outcome measure was the occurrence of PF, defined by a 2-point increase in the worst pain score after radiation therapy compared with baseline without a decrease in analgesic intake or a 25% increase in analgesic intake without a decrease in worst pain score.[9] We considered a PF early in onset if it started on days 2 to 5 and late if it started on days 6 to 14. PF was distinguished from pain progression by requiring the worst pain score and/or analgesic intake to return to baseline levels before or on day 14. If this was not the case, pain was classified as pain progression. Secondary outcomes were pain scores on days 1 to 14 and 28, side effects of the study medication, and quality of life.

Statistical analysis

The study was designed as a superiority study assuming a reduction of 50% (from 40% to 20%) of the occurrence of PF by administering 4 × 8 mg dexamethasone compared with placebo.[10] We expected a dropout of 20% and 2 years to complete the trial. Assuming a 90% power (beta = 0.1) and 2-sided alpha of 5%, a total of 411 patients was necessary. Because of slow accrual, the protocol was amended after 3 years to change the beta to 0.2. A sample size of 294 patients (98 per group) was then required.

After publication of the NCIC CTG SC 23 study, we decided to perform intention-to-treat and sensitivity analyses in line with the NCIC CTG SC.23 analyses to be able to compare the results.[4] Patients who had received at least 1 fraction of radiation therapy were evaluable irrespective of intake of study medication. For the intention-to-treat analysis, we assumed that patients who were not assessable owing to missing data had experienced a PF. We also performed a sensitivity analysis assuming that patients with missing pain scores did not have a PF.

To study the influence of missing data on outcome, we calculated PF incidence leaving out patients with missing data. We used the Fisher exact test for comparison of the percentages of occurrence of PF and the timing of PF among the 3 groups. Differences in duration of PF were assessed with a 1-way analysis of variance on the log-transformed durations. To check for influence of changes in opioid intake, we calculated median cumulative oral morphine equivalence doses during the first 14 days and interquartile ranges (IQRs) and compared those using analysis of variance. To check for influence of fractionation on PF incidence, we compared the incidence of PF for the patients receiving a single fraction of 8 Gy versus those receiving 20 Gy in 5 fractions using the Fisher exact test. Changes over time in mean pain scores, study medication side effects, and quality of life scores for all groups were analyzed using linear mixed models with fixed effects for treatment group, time (using B-splines to account for nonlinear trends over time), and their interaction, as well as a random intercept and random slope for time per subject. The treatment × time interaction was tested using the likelihood ratio test. In case of significant interactions, post hoc tests were used to compare the treatment groups on day 1 (second day of intake study medication), day 4 (first day without study medication), and day 9 (any effect of study medication washed out). All analyses were done with SAS, version 9.4. All P values were 2-sided.

Results

From January 2012 to April 2016, 295 patients were randomized (Fig. 1). Patient characteristics are described in Table 1. In patients using pain medication, the use of opioids at randomization was 45% (38 patients) in group A, 56% (41 patients) in group B, and 49% (41 patients) in group C. The number of patients not assessable for PF incidence within the first 14 days was 20 in group A, 17 in group B, and 27 in group C (Fig. 1). In total, 38 patients had missing data.

In the intention-to-treat analysis, 103 patients experienced a PF within the first 14 days: 38 (38%) in group A, 26 (27%) in group B, and 39 (39%) in group C (P = .07) (Table 2). The percentages of patients with no PF and no pain progression were 48% in group A, 50% in group B, and 37% in group C. When patients with missing data (n = 38) were censored, the percentages of patients experiencing

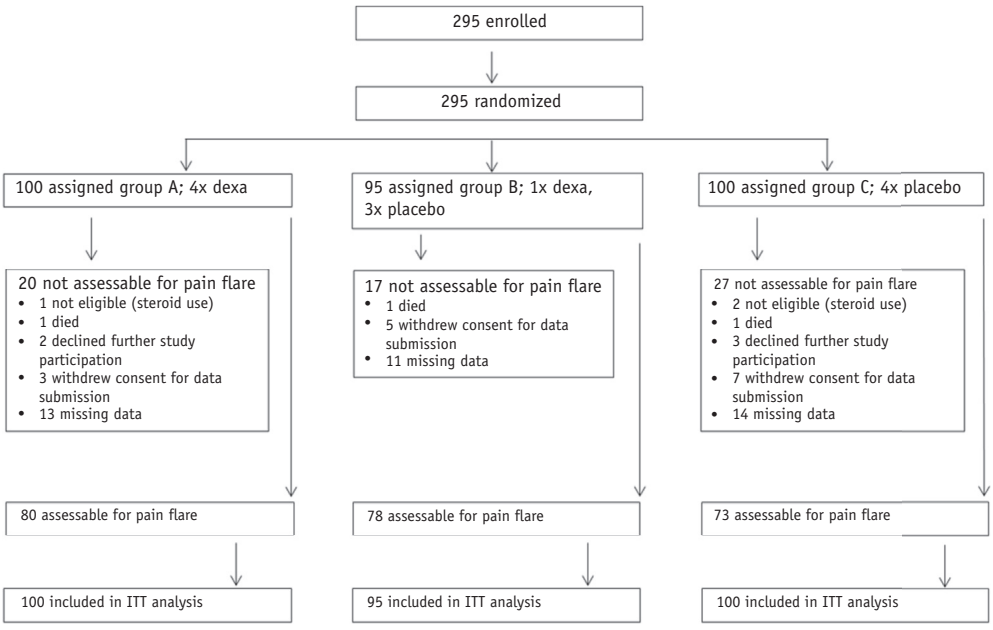

Fig. 1. Trial profile. Missing data refer to patients without a complete 14-day pain diary.

a PF within 14 days were comparable: 38.5% in group A, 23% in group B, and 38.5% in group C ($P = .07$).

In the sensitivity analysis, assuming that patients with missing pain scores did not have a PF, 65 patients experienced a PF within the first 14 days: 25 patients (25%) in group A, 15 patients (16%) in group B, and 25 patients (25%) in group C ($P = .09$). The percentages of patients with no PF and no pain progression were 61% in both group A and group B and 51% in group C. In group A, 52% of the PFs occurred on days 2 to 5, compared with 73% in group B and 88% in group C ($P = .02$). The mean duration of the PF was 2.1 days in group A, 4.5 days in group B, and 3.3 days in group C ($P = .0567$).

Figure 2 depicts the course of pain during the 14 days after the start of radiation therapy and at day 28, showing statistically significant differences in the course of pain for the 3 groups ($P < .001$). On day 1, patients in groups A and B had significantly lower scores than those in group C ($P = .0107$ and .0244, respectively). On day 4, patients in group A had a lower mean score than those in groups B and C ($P = .0121$ and .0217, respectively). No statistically significant differences were found among the groups on day 9.

The median cumulative oral morphine equivalence dose was 317 mg (IQR, 125-919) in group A, 421 mg (IQR, 127-1039) in group B, and 374 mg (IQR, 205-954) in group C during the 14 days after radiation therapy. The difference in oral morphine equivalence doses among the 3 treatment groups was not significant ($P = .28$).

Of the 233 patients receiving a single fraction of 8 Gy, 36% experienced a PF and 46% no PF in the intention-to-treat analysis, versus 27% PF and 51% no PF among 41 patients receiving 20 Gy in 5 fractions ($P = .52$). In the sensitivity analysis, these percentages were 23% with a PF and 59% with no PF after single-fraction 8 Gy versus 22% PF and 56% no PF after 20 Gy ($P = .72$).

During the study period, 12 serious adverse events were reported (9 hospital admittances and death in 3 patients), mostly caused by deteriorating condition. All were determined to be unrelated to the study medication.

The compliance rates for the EORTC-QLQ-C15 PAL and BM22 quality of life questionnaires were similar among the 3 arms, varying from 74% to 88%. Except for pain and functional interference, no clear changes over time were observed (Figs. E3 and E4). Mean pain scores (EORTC QLQ-C15 PAL and BM22) decreased by about 10 to 15 points, and median scores for functional interference (EORTC QLQ-BM22) improved by about 10 points. The median scores for overall quality of life and physical functioning (C15 PAL) varied, approximately 60 and 80, respectively, and remained stable. Nausea score (EORTC QLQ-C15 PAL) varied, approximately 10, and remained stable. There were no statistically significant differences for most of the quality of life scales and items.

Regarding the additional questions on medication side effects, patients in group A experienced significantly more restlessness on day 5 than did patients in group C ($P = .02$) (Fig. E5). The difference in appetite between groups A and B was significant on day 5 ($P = .004$). All effect sizes, however, were small.

Discussion

In our randomized study of 295 patients with painful bone metastases, we did not find a statistically significant effect of 2 dose schedules of dexamethasone on the incidence of PF after palliative radiation therapy or on the duration of PF. In the intention-to-treat analysis, a PF occurred in 38%

Table 1 Patient characteristics by randomization group

	Group A Dexamethasone days 0-3 (N = 100)		Group B Dexamethasone day 0, placebo days 1-3 (N = 95)		Group C placebo days 0-3 (N = 100)	
	n	%*	n	%	n	%
Sex						
Male	61	62	51	54	61	62
Female	38	38	43	46	38	38
Missing	1		1		1	
Age						
Mean, y	67		65		68	
Range, y	30-84		40-91		44-85	
Missing, n	1		1		1	
Karnofsky Performance Status Scale score						
90-100	29	30	27	29	27	28
70-80	52	53	51	55	54	56
40-60	17	17	15	16	16	17
Missing	2		2		3	
Primary tumor						
Prostate	30	30	24	25	29	30
Breast	27	27	27	29	22	23
Lung	17	17	21	22	24	25
Other	25	25	22	23	21	22
Missing	1		1		4	
Current other treatments						
None	30	32	35	41	42	46
Chemotherapy	13	14	9	11	10	11
Antihormonal therapy	38	40	27	31	31	34
Bisphosphonates	3	3	3	4	0	0
Combination	11	12	12	14	9	10
Missing	5		9		8	
Use of pain medication at randomization						
No	14	14	21	22	14	14
Yes†	85	86	73	78	83	86
Missing	1		1		3	
Worst pain score at randomization						
Mean	6		6		5	
7-8	47	48	44	47	39	40
5-6	25	25	30	32	27	27
2-4	26	27	19	20	32	33
Missing	2		2		2	
No. of fractions						
1 × 8 Gy	75	77	78	83	80	81
5 × 4 Gy	16	17	13	14	12	12
6 × 4 Gy	1	1	1	1	0	0
Other‡	5	5	2	2	6	6
Missing	3		1		1	
Previous radiation therapy on other bone metastases						
Yes	11	16	15	21	12	17
No	59	84	55	79	57	83
Missing	30		25		31	

* Due to rounding of decimals, totals can add up to less or greater than 100%.

† Intake of any pain medication, paracetamol, neuropathic pain medication, opioid, or nonsteroidal anti-inflammatory pain medication reported at randomization.

‡ Five, 2, and 6 patients in groups A, B, and C, respectively, received other schedules, namely 2 × 8 Gy, 3 × 4 Gy, or 4 × 4 Gy.

Table 2 Incidence of pain flare within the first 14 days after randomization, intention-to-treat and sensitivity analysis

	Group A dexamethasone days 0-3 (N = 100)	Group B dexamethasone day 0 placebo days 1-3 (N = 95)	Group C placebo days 0-3 (N = 100)	*P* value (2-sided)
Intention-to-treat analysis*				
Not assessable†	7 (7%)	6 (6%)	13 (13%)	.07
No pain flare and no pain progression	48 (48%)	47 (50%)	37 (37%)	
Pain progression	7 (7%)	16 (17%)	11 (11%)	
Pain flare	38 (38%)	26 (27%)	39 (39%)	
Sensitivity analysis				
Not assessable	7 (7%)	6 (6%)	13 (13%)	.09
No pain flare and no pain progression	61 (61%)	58 (61%)	51 (51%)	
Pain progression	7 (7%)	16 (17%)	11 (11%)	
Pain flare	25 (25%)	15 (16%)	25 (25%)	

* Data on pain scores during follow-up were missing in 13 patients in group A, 11 patients in group B, and 14 patients in group C. In the intention-to-treat analysis these patients were considered to have experienced a pain flare; in the sensitivity analysis these patients were considered to have experienced no pain flare.

† Patients were considered not assessable for both analyses only if they were not eligible due to steroid use, died, declined further participation, or withdrew consent within the first 15 days (7 patients in group A, 6 patients in group B, and 13 patients in group C).

of patients receiving 4 daily doses of 8 mg dexamethasone and 39% of patients receiving 4 daily doses of placebo. Surprisingly, the lowest PF incidence (27%) was observed in patients receiving 1 dose of dexamethasone 8 mg followed by 3 daily doses of placebo. However, these differences were not statistically significant ($P = .07$). If patients with missing data were assumed not to have had a PF (sensitivity analysis), there were still no significant differences among the 3 groups.

A recent review including 7 prospective studies on PF incidence (using comparable definitions of PF) after external beam radiation therapy reported PF percentages ranging from 2% to 44% without intake of dexamethasone.[3] A phase 2 study included in the review reported a 24% incidence of PF in 23 patients receiving 8 mg dexamethasone orally before a single dose (8 Gy) of radiation therapy,[10] seemingly lower than the 41% incidence found in a previous study in 44 patients not receiving dexamethasone.[9] Another nonrandomized study in the review reported a PF within 10 days in 22% of 41 patients receiving a single 8-Gy fraction in combination with 8 mg dexamethasone orally before radiation therapy and for 3 consecutive days after treatment.[11]

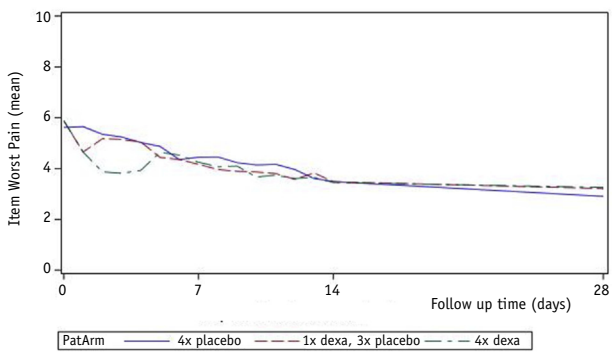

Fig. 2. Course of pain. Mean worst pain scores during the study period. Of note, day 0 is the first day with intake of medication and start of the radiation therapy. The first 14 days are daily measurements (days 0-14), with a last measurement on day 28.

The lowest percentages were reported in a double-blind randomized study in 120 patients with vertebral metastases receiving either a 24-hour infusion of 5 mg/kg methylprednisolone or placebo before radiation therapy.[12] A significant effect on incidence (6.6% vs 20%) and mean duration (1.25 vs 3.75 days) of PF was seen in patients receiving methylprednisolone.

In the previously mentioned NCIC SC23 trial, 298 patients with painful bone metastases from solid tumors receiving a single 8-Gy dose were randomized to receive either 8 mg dexamethasone or placebo orally before radiation therapy and then 4 days thereafter.[1] In the intention-to-treat analysis, assuming that patients with missing data (n = 22) had had a PF, a PF within the first 10 days occurred in 26% of patients receiving 5 doses of dexamethasone versus 35% of patients receiving placebo (1-sided $P = .05$). In the sensitivity analysis, assuming that patients with missing data had had no PF, the percentages were 18% and 29%, respectively ($P = .01$). The median duration of the PF was 3 days in the dexamethasone group and 2 days in the placebo group. Differences in mean pain scores per day were not reported.

For patients receiving one 8-mg dose of dexamethasone followed by placebo (group B) or only placebo (group C), our results are comparable to the study arms in the NCIC trial[4] (Table 3). The lack of statistical significance for the difference between these 2 groups in our study may be explained by the relatively low power of our study, which we were forced to lower when accrual

Table 3 Comparison of the 2 randomized pain flare trials on dexamethasone; NCIC CTG SC 23 and Dutch DEXA study.

NCIC CTG SC23				Dutch DEXA			
	Intention-to-treat analysis pain flare	Sensitivity analysis pain flare	Duration of pain flare (median)		Intention-to-treat analysis pain flare	Sensitivity analysis pain flare	Duration of pain flare (mean)
Dexamethasone 5 × 8 mg	26%	18%	3 d	Dexamethasone 4 × 8 mg (group A)	38%	25%	1.5 d
				Dexamethasone 1 × 8 mg Placebo 3× (group B)	27%	16%	4.5 d
Placebo 5×	35%	29%	2 d	Placebo 4× (group C)	39%	25%	3.3 d
Study design and criteria				Study design and criteria			
Superiority study				Superiority study			
One-sided alpha 0.05, power 90%				Two-sided alpha 0.05, power 80%			
Intake of NSAIDs not allowed				Intake of NSAIDs allowed			
Total dose dexamethasone 40 mg in study arm				Total dose dexamethasone maximum 32 mg in group A			
10-d follow-up daily pain scores and on day 42				14-d follow-up daily pain scores and on day 28			
EORTC PAL15 and BM22 QoL questionnaires on days 0, 10, and 42				EORTC PAL15 and BM22 QoL questionnaires on days 0, 7, 14, and 28			

Abbreviation: NSAIDs = nonsteroidal anti-inflammatory drugs.

remained low. However, the unexpected results in group A receiving 4 doses of 8 mg dexamethasone are difficult to explain. In both the intention-to-treat and sensitivity analyses, the occurrence of PF in this group is almost identical to that of the placebo group C and very different from the results of the NCIC trial. There were no remarkable differences among patients in groups A, B, or C that might explain the difference in incidence of PF. A PF occurred much more often (38% of group A patients) than in the study by Hird et al,[11] who used the same dexamethasone dosages and found an incidence of only 22%, comparable to the NCIC outcome (26%). We have no good explanation regarding why in our study a single dose of 8 mg seemed more effective than 4 daily doses of 8 mg dexamethasone in the prevention of PF. A remarkable finding was the relatively high percentage (17%) of patients in group B with pain progression. In contrast, in groups A (4 × dexamethasone) and C (4 × placebo), pain progression was observed in only 7% and 11% of patients, respectively.

In this study, both dexamethasone schedules significantly postponed the occurrence of PF compared with placebo. This effect was also observed in NCIC SC23. In addition, treatment with dexamethasone resulted in significantly lower pain scores on day 1 (groups A and B) and day 4 (group A only) compared with placebo, implying a direct analgesic effect. In NCIC SC23 the authors reported a mean reduction in pain score for days 0 to 5 favoring the dexamethasone group (−1.79 vs −1.09, $P = .01$). A recent review on the effect of corticosteroids on cancer pain also reported an analgesic effect, although moderate.[13]

Treatment with dexamethasone was well tolerated in this study. Patients in group A reported a small, but significant, increase in appetite, which may be a welcome side effect in advanced cancer. They also reported a higher level of restlessness on day 5, compared with placebo. The NCIC trial described improvement in scores for nausea, functional interference, and appetite. In this study, the opposite was seen: Nausea was lower in patients using only placebo. Except for pain and functional impairment, there were no significant changes in the quality of life subscales and items over time in any of the arms.

The NCIC trial reported a number needed to treat to prevent a PF of 11 for the intention-to-treat and 9 for the sensitivity analysis.[4] The researchers concluded that because of the additional improvement in quality of life items, the prophylactic use of dexamethasone should be adopted as standard of care for patients receiving palliative radiation therapy for painful bone metastases. If our results are seen from the perspective of not having a PF or pain progression, a trend for a beneficial effect of dexamethasone becomes visible: 48% had no PF or pain progression in group A and 50% in group B versus 37% in group C in the intention-to-treat analysis. In the sensitivity analysis, these percentages were 61% in groups A and B versus 51% in group C. To prevent PF or pain progression, we estimate a number needed to treat of 9 based on the intention-to-treat analysis and 10 based on the sensitivity analysis.

Although we allowed patients to undergo either an 8 Gy single-fraction or multiple-fraction radiation therapy, there

was no difference in the incidence of PF among the 3 groups. Hird et al reported similar PF incidences after 8-Gy single-fraction or 20 Gy in 5 fractions in 111 patients: 39% and 41%, respectively.[14]

The main limitations of this study are its lack of statistical power and the considerable number of missing pain scores. During the study period we adjusted the power from 90% to 80%, owing to slow accrual of patients. This relatively low power, together with the unexpected and unexplained high incidence of PF in group A, may explain the lack of statistical difference for the occurrence of PF in the first 2 weeks after treatment. Sixty-four patients (22%) were not assessable, 38 because of missing pain scores in the pain diary and 26 mostly owing to early death, declining further study participation, or withdrawal of consent; this reflects both the very vulnerable patient population and problems inherent to studies using repeated questionnaires. It is unlikely that dropout was influenced by the allocated treatment. The lack of a statistical difference between the groups may also be a false-negative finding.

A recent debate on the use of dexamethasone to prevent PF concluded that consensus for routine use could not be achieved, and the choice to use dexamethasone prophylactically is a shared decision between radiation oncologists and patients.[15] Factors including symptom burden, comorbidities, performance status, quality of life, and radiation dose and fractionation should be considered on an individual level.

Conclusions

Prophylactic intake of dexamethasone had no clear effect on reducing PF incidence after radiation therapy for painful bone metastases, although an immediate effect on pain was observed. Repeat studies should be performed to solve the discrepancy between the results of this study and previous results. In addition to prevention of PF, the mechanisms of direct pain reduction in combination with palliative radiation therapy should be a topic of further dose-effect studies, identifying optimal doses of dexamethasone intake and the optimal duration.

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