Short communications

Nuclear Medicine Review 2006
Vol. 9, No. 2, pp. 138–143

ISSN 1506–9680

VIA MEDICA

The effects of radioisotope therapy and radiotherapy in subjects with breast cancer with bone metastases

Małgorzata Djabełek-Maciaś[1], Iwona Wiśniewska[1], Maria Ochman[1], Andrzej Kołodziejczyk[2], Jacek Żebrowski[2], Piotr Piwkowski[2]

Division of Radiotherapy, Lower Silesian Oncology Centre, Wrocław[1], Poland; Department of Nuclear Medicine, 4th Military Clinical Hospital, Wrocław[2], Poland

[Received 16 V 2006; Accepted 23 XII 2006]

Abstract

BACKGROUND: Metastatic bone disease is found in 80–90% of patients examined after death and is a serious problem in everyday practice. The aim of the study was the evaluation of the survival time of patients with bone metastases in relation to the prognostic group and applied treatment.

MATERIAL AND METHODS: The authors analyzed 84 patients treated in the Radiotherapy Division of Lower Silesian Oncology Centre during the years 1997–2004. Radioisotope treatment was conducted in the Department of Nuclear Medicine of the 4th Military Clinical Hospital in Wrocław. The average age of the patients was 53.1 years. The women differed in staging at the moment of diagnosis. The patients were divided into two groups with different clinical prognoses. In addition to systemic treatment (biphosphonates, chemotherapy or hormonotherapy), 32 (38.1%) patients were treated with teletherapy and 20 (23.8%) underwent radioisotope therapy. In 32 (38.1%) patients both methods were applied. The analysis of results included the estimation of overall survival (OS) meaning the time of survival from the onset of disease to one of the end points. End points of the observation were defined by the authors as the patient's death or last control visit. The Kaplan-Meier method was used.

RESULTS: The outcomes of the observation are closely connected with particular prognostic groups. The Kaplan-Meier's diagrams presented here indicate that teletherapy combined with radioisotope therapy was the most beneficial for the patients with metastases in bones and other organs.

CONCLUSIONS: The best effects of the treatment measured by overall survival were obtained with combined treatment: radiotherapy and radioisotopes, in the group with bone and extra-skeletal metastases.

Key words: bone metastases, breast cancer, bone pain, radiopharmaceuticals

Correspondence to: Małgorzata Djabełek-Maciaś
Dolnośląskie Centrum Onkologii
Pl. Hirszfelda 12, 53–413 Wrocław, Poland
Tel: (+48) 71 368 94 57
e-mail: ochman.m@dco.com.pl

Introduction

The treatment of bone metastases in the course of breast cancer is a serious challenge for contemporary oncology. Bone metastases occur in about 25–30% of all breast cancer cases and 80% of advanced cases [1]. To estimate the scale of this problem we have to take into consideration the fact that about one million new diagnoses of breast cancer are made every year, and about 400,000 women die annually from this neoplasm. The advances achieved in treating patients with neoplasms have also changed the attitude to women with bone metastases. Treating these patients means not only the alleviation of pain but also restoration of their physical activity and, not infrequently, prolongation of life. The prognosis in the case of bone metastases is unfavourable. The presence of metastases means generalization of the disease and in most cases determines the fate of the patient. Although breast cancer patients with bone metastases live longer (on average 2 years) than women with another distant metastases localization, only about 10% of these patients live 5 years or longer from the time the diagnosis is made [1, 2].

In about 70% of cases bone metastases are accompanied by pain that requires treatment [1]. Menacing complications are pathological fractures, paralyses and pareses resulting from spinal cord or nerve radices compression. 10–20% of patients suffer from hypercalcaemia [1]. All subjects present a considerable decrease in quality of life and depressive states.

The main method of bone metastasis treatment is systemic therapy combined with local and symptomatic therapy. The combined treatment is a multidisciplinary therapy [1, 3–4, 5–8]. Radiotherapy has been an acknowledged method of bone metastasis treatment for many years. Palliative irradiation reduces pain ailments in about 85% of cases, and in 50% of cases accomplishes total pain remission [1]. The analgesic effect appears within the first days after the beginning of radiotherapy and lasts for about 30 weeks [1, 9]. Currently the role of radioisotope therapy as a separate method and a combined one with radiotherapy in disseminated bone metastases treatment is increasing [3, 10, 11–17]. The number of orthopaedic operations in patients with complications from bone metastases is increasing. Proper analgesic medication and overcoming other symptoms of disseminated neoplasmatic disease are very important as well [1].

The aim of the study was to evaluate survival time in patients with confirmed bone metastases in the course of breast cancer in relation to the prognostic group and radiotherapeutic methods applied.

Material and methods

The evaluated group consisted of 84 women treated in the Division of Radiotherapy, Lower Silesian Oncology Centre during the years 1997–2004. Radioisotope therapy was conducted in the Department of Nuclear Medicine, 4th Military Clinical Hospital in Wrocław. Primarily the patients differed in clinical staging. Grade I was confirmed in 4 patients (4.7%), grade II in 44 patients (52.3%), grade IIIA in 8 patients (9.5%), grade IIIB in 8 patients (9.5%) and grade IV in 8 patients (9.5%). 12 patients had unknown primary clinical staging, but grade IV was excluded (Figure 1).

Bone metastases appeared at different periods of time after neoplasmatic disease was diagnosed. The median of time when bone metastases were found differed depending on clinical staging and was presented as follows: grade I on average after 55.5 months, grade II on average after 34 months, grade IIIA on average after 28.5 months and grade IIIB on average after 23 months (Figure 2).

For the purposes of the study the patients were divided into two groups with different clinical prognoses.

The first group (38 subjects) comprised only of women with bone metastases.

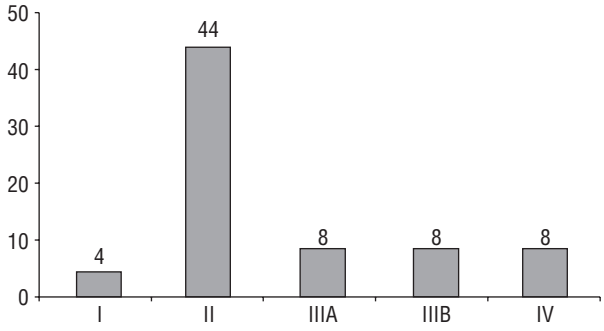

Figure 1. Graphic display of clinical staging.

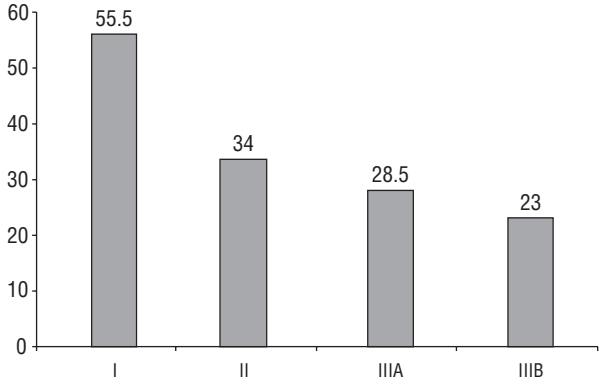

Figure 2. Graphic presentation of the median of time from breast cancer diagnosis to bone metastases appearance in months.

The second group (46 subjects) comprised of women with metastases in parenchymatous organs or local recurrence apart from bone metastases.

All subjects, after bone metastases recognition, underwent treatment that fulfilled oncological standards and included hormonotherapy or chemotherapy, bisphosphonates and analgesic drugs medication. Bone metastasis presence was confirmed with radiographic examination and/or bone scintigraphy.

The results were analyzed with the use of the Kaplan-Meier method. The authors evaluated the overall time of survival (OS) measured from the date of breast cancer diagnosis to the end point. The authors defined an end point as the death of the patient or the date of the last control visit for living patients.

Groups characteristics

The first group contained 38 women with bone metastases only. The average age was 58.5 years (range 39 to 73). 25 of the patients were in postmenopausal period. The most frequent histological type was the invasive ductal carcinoma (71% of cases), lobular invasive carcinoma (13.2% of cases) or other histological types (15.8% of cases). The average time from diagnosis to finding bone metastases was 31 months in this group (range 0–126 months). 70% of the patients presented bone lesions in two, three or more localizations. The most common localizations were the vertebral column and pelvis. Long and flat bones were not so often affected. Most of the metastases were presented as osteolytic lesions in RTG.

The second group, with 46 patients, presented metastases in bones and parenchymatous organs or local recurrence. The average age in this group was 48 years (range 36–71). This group also showed a prevalence of ductal invasive carcinoma present in 82.6% of cases. The rest of the histological types presented as follows: lobular invasive carcinoma — 6.5% of cases and other histological types 10.9% of cases. 32.6% of women were in postmenopausal period. Bone metastases appeared in this group as the first or successive metastatic localization. The median of time from breast cancer diagnosis to bone metastases onset was 37.5 months (range 0–264). The liver was the most often affected parenchymatous organ (17 subjects). Lung metastases were revealed in 8 patients, brain metastases in 4 patients, local recur-

rence in 6 patients, multiple localizations in 9 patients and other localizations in 2 patients. By synchronic metastases the authors meant metastatic changes in osseous and extra-osseous localizations at the time of diagnosis. Metachronic metastases were considered when the time of finding metastases in bones was different (usually earlier) from the moment of diagnosing metastases in parenchymatous organs (Table 1).

Similarly to the first group bone metastases were mostly osteolytic lesions present in two or more localizations. Both groups are characterized in Table 2.

Table 1. Synchronic and metachronic metastases

Localization of metastasis	Metastases	
	Synchronic (no. of pts)	Metachronic (no. of pts)
Lung	7	1
Liver	3	14
Local recurrence	4	2
Brain	0	4
Multiple metastases	2	7
Others	0	2

Applied treatment

In both groups, apart from systemic treatment, radiotherapy (32 subjects — 38.12%), radioisotope therapy (20 subjects – 23.8%) or both methods (32 subjects — 38.1%) were introduced (Table 3).

In the group of patients who underwent only radiotherapy, irradiation was applied to localizations with the highest pain intensity. Various fractionation schemes were used.

18.7% of the patients received a single fraction of 6 Gy or 8 Gy, whilst 71.3% of the patients received fractionated radiotherapy. A dose of 20 Gy was applied in 5 fractions, 21 Gy in 7 fractions or 30 Gy in 10 fractions. The quantity of fractions and applied dose depended on general patient condition, extensiveness and localization of metastases, predicted survival time and coexistent treatment. Radiotherapy was conducted using a Theratron device with gamma ^{60}Co rays, Philips device with X rays and photon radiation with energy of 4–6 MeV obtained in linear accelerators (Neptun device, Co-line, CLINAC) [18–23]. Before the irradiation began, the target area was marked with the use of a simulator (Roentgen device with optional TV view). Subsequently, a physicist carried out the necessary calculations. Because of a lack of acknowledged guidelines concerning irradiation area margins, the authors used the area two vertebrae above and two vertebrae below the lesion for metastases localized in the vertebral column. For other localizations the irradiated area covered a visually de-

Table 2. Clinical characteristics of evaluated groups

Feature	Number of patients (%)	
	Patients with bone metastases only (group I)	Patients with bone and extra osseous metastases (group II)
Number of patients in particular groups	38	46
Age		
Median	58.5	48
Range	39–73	36–71
Clinical staging		
I	3 (7.9%)	1 (1.2%)
II	19 (50%)	25 (54.3%)
IIIA	2 (5.3%)	6 (13%)
IIIB	4 (10.6%)	4 (8.7%)
IV	3 (7.9%)	5 (10.9%)
Unknown	7 (18.4%)	5 (10.9%)
Histopathological diagnosis		
Invasive ductal carcinoma	27 (71%)	38 (82.6%)
Invasive lobular carcinoma	5 (13.2%)	3 (6.5%)
Others	6 (15.8%)	5 (10.9%)
Menopausal statu		
Pre-menopausal	13 (34.2%)	31 (15%)
Post-menopausal	25 (65.8%)	67.4 (32.6%)

Table 3. Modes of applied treatment

	Number of patients (%)		
	Teletherapy	Radioisotope	Teletherapy and radioisotope
Patients with bone metastases only (group I)	8 (21%)	15 (39.5%)	15 (39.5%)
Patients with bone and extra osseous metastases (group II)	24 (52.2%)	5 (10.9%)	17 (36.9%)

fined lesion with 2 cm margins. If a bone presented multiple metastases, the target area covered the whole bone.

An important issue in radiotherapy planning is dose specification. To avoid under dosing in lesions localized deep under the skin's surface such as the lumbar part of vertebral column, the dose was not specified as a so called "maximum", but at a particular depth.

In 20 subjects only radioisotope therapy was applied, whereas 32 women underwent both radiotherapy and radioisotope therapy.

The patients who qualified for radioisotope therapy had documented foci of increased osseous metabolism by means of scintigraphy confirmed by another diagnostic method (RTG, CT or NMR). The patients were subjected to a special therapeutic protocol concerning blood smear parameters. Minimal values presented as follows: WBC > 3.0G/L, platelet count > 100.000/μl, creatinine level < 1.5 mg/dl.

Pregnancy, breast feeding and spine compression symptoms were contraindications for radioisotope therapy. Radioactive isotope could not be administered before two weeks following chemotherapy or bisphosphonate application [15].

^{153}Sm with an activity of 1 mCi/kg b.w. or ^{89}Sr with an activity of 4 mCi were administered. 52 patients underwent 120 radioisotope therapies in total (105 with ^{153}Sm and 15 with ^{89}Sr). The number of doses of radioisotope received by one patient ranged from 1 to 6. 16 women received a single radioisotope treatment, 16 patients received two, 12 patients received 3 doses, 5 patients 4 doses, 2 patients 5 doses and 1 woman received 6 doses.

In patients who underwent teletherapy as well as radioisotope therapy, the rules concerning treatment planning, margins and doses were the same as described in the group treated only with radiotherapy.

Results

The analysis of overall survival time and the time from bone metastases to death or the date of the last control visit for living patients was made. The data was evaluated with the use of the Kaplan-Meier curve, the time was estimated in months.

Observation results are closely associated with particular prognostic groups. The Kaplan-Meier diagrams (Figures 3–6) show that the greatest benefit from the combined therapy (external beam radiotherapy and radioisotope therapy) was shown both in patients with osseous and extra osseous metastases.

Discussion

The longer survival times in patients with bone and extra osseous metastases who underwent the combined therapy may result from applied systemic treatment. The application of chemotherapy followed guidelines for patients with extra osseous metastases. Chemotherapy applied in patients with disseminated breast carcinoma lengthens the stabilization period and time to progression and improves the quality of life and survival time. This has been proved by many randomized studies which evaluated cytostatic treatment in metastatic breast cancer [24, 25]. The advantage of external beam radiotherapy and radioisotope therapy association in patients with bone metastases in the course of breast cancer has been stated [26]. Most randomized studies

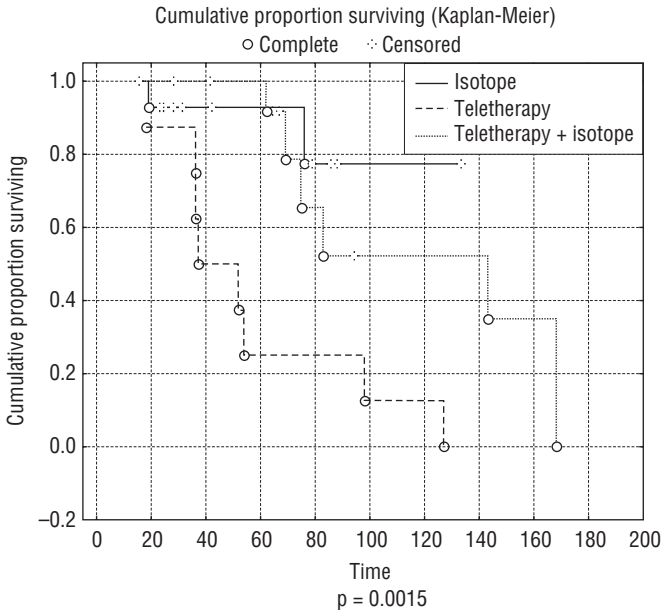

Figure 3. Overall survival time (OS) from breast cancer diagnosis to death or the last control visit in living patients in the group with bone metastases (group I).

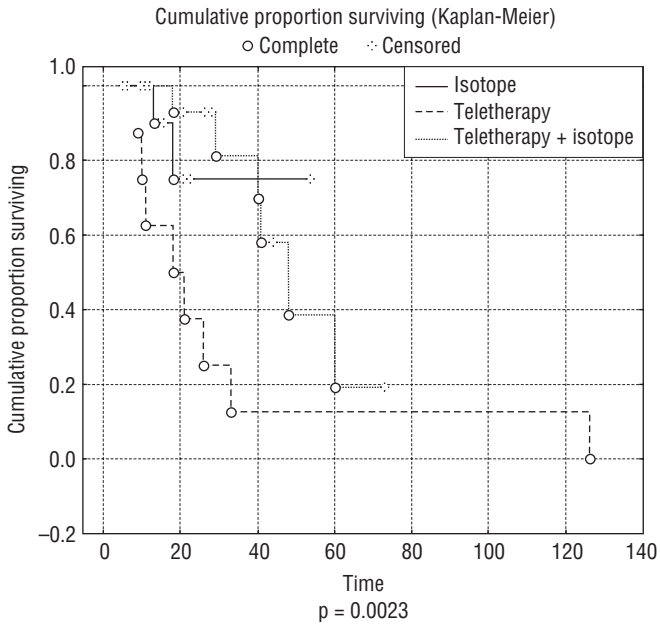

Figure 4. Survival time from bone metastases diagnosis to death or the last control visit in living patients with bone metastases only (group I).

that compared radioisotope therapy to radiotherapy or cytostatic treatment concerned patients with bone metastases in the course of prostate cancer. These studies showed greater efficacy of combined treatment for pain ailments and life quality improvement [17].

The group of patients with metastases localized only in the skeletal system presented worse effects. This can result from the presence of negative oestrogen and progesterone receptors and

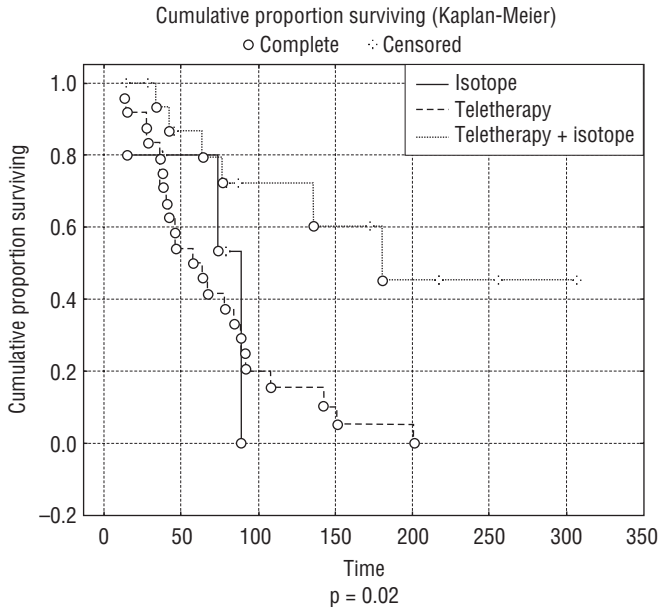

Figure 5. Overall survival time (OS) in patients from breast cancer diagnosis to death or the last control visit for living patients in group with bone and extra-osseous metastases (group II).

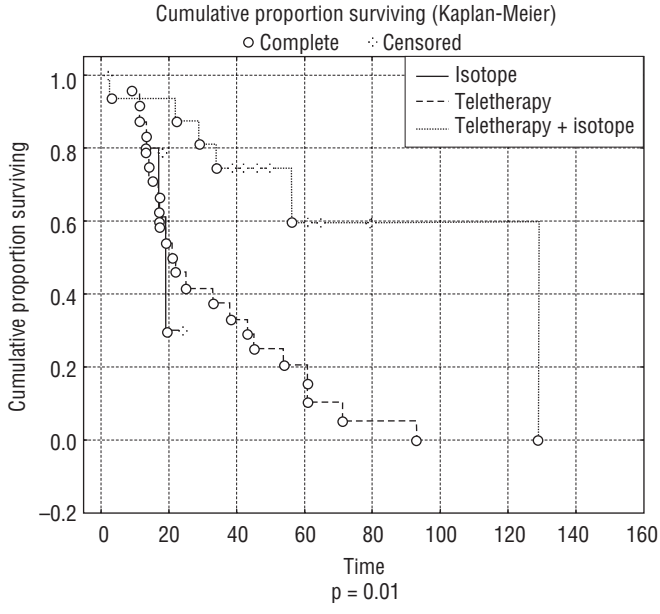

Figure 6. Survival time from bone metastases diagnosis to death or the last control visit for living patients in group with bone and extra osseous metastases (group II).

the application of inadequate systemic treatment. At the time these patients were treated progesterone and oestrogen receptor designating was not a routine procedure. The presence of these receptors is a predictive factor for response to systemic treatment.

In patients with advanced breast cancer expressing oestrogen receptors palliative treatment, including hormonotherapy, gives results comparable with chemotherapy. At the moment of bone metastasis appearance hormonotherapy was applied. As randomized studies and meta analysis show, the response to this treatment could concern only about 10% of receptor negative patients [27–28].

Conclusions

The authors achieved the best effects with the combined treatment: radiotherapy and radioisotopes, in patients with bone and extra skeletal metastases.

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