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Palliative radio-chemotherapy with ifosfamide and BCNU for breast cancer patients with cerebral metastases*

A 5-year experience

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Summary. Between January 1983 and April 1989, 61 patients with brain metastases of primary breast cancer were treated in the Robert Janker Clinic. To optimize the overall response rates, a simultaneous combination of radiation and chemotherapy was used. The patients median age was 49 (range, 30–67) years and the median performance score, 1 (0–2). The average interval between the diagnosis of the primary tumour and the brain metastases was 38 (range, 3–144) months. A total of 82% of the patients had multiple cerebral metastases. All patients had been pretreated with primary surgery; 79%, with radiation; 74%, with chemotherapy; and 64%, with hormones. Radiotherapy was given using a cobalt 60 machine. The whole brain was irradiated in daily fractions of 1.5 Gy, up to a total dose of 45 Gy. Using a split-course technique, this dose was given in three courses simultaneously with the chemotherapy. The chemotherapeutic regimen consisted of ifosfamide given daily for 5 days at 2 g/m^2 and the nitrosourea derivative carmustine (BCNU) given at 30 mg/m^2 on 3 days. The toxicity of the treatment was moderate; no haemotological or gastro-intestinal complications occurred. Complete and mostly irreversible alopecia occurred in all cases. All patients received a cranial computerized tomographic (CT) scan prior to and after treatment. According to the criteria of the International Union Against Cancer (UICC), there was a complete remission (CR) in 20% of the patients and a partial remission (PR) in 45%; 20% had a minor remission (MR) and 7% showed no change (NC) in the tumour. Another 7% of the patients experienced a progression of their metastases (PD). The median survival was 8 months for all patients and 12 months for those showing a CR.

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Introduction

Palliation of neurological symptoms caused by cerebral metastases of breast cancer remains an important challenge to both radiotherapists and medical oncologists. Secondary brain tumours are in most cases caused by lung and breast cancer and are diagnosed much more frequently today than a decade ago [2]. This may be due to longer survival of the patients, whose primary tumours and metastases can now be treated more successfully by improved surgical and radiotherapeutic techniques and, most importantly, by combinations including hormonal and cytotoxic treatment regimens [11, 18].

Early detection of cerebral metastases is made possible by the frequent or routine use of sophisticated radiological imaging techniques such as computerized tomography (CT) and magnetic resonance tomography (MRT) [1]. About 80% of patients show multiple brain metastases, sometimes accompanied by meningeal carcinomatosis, such that neurosurgery should be an exceptional event [3, 9, 11, 22].

Radiotherapy is a useful method for the management of cerebral metastases and can also be applied if metastases are present in other organs. Alleviation of the neurological symptoms can be achieved by a reduction in the cerebral pressure, whereas objective remissions of the tumour mass are relatively rare after the exclusive use of radiation. The median survival of these patients is 3–6 months [2, 6, 10, 19, 20], which is an improvement in comparison with that obtained by symptomatical treatment with diuretics and cortisone, during the course of which patients die after approximately 1–3 months [5].

Cytotoxic drugs used in the treatment of brain metastases should be able to pass the blood-brain barrier [11, 25]. The most effective substances are the nitrosourea derivatives. The use of nimustine (ACNU), carmustine (BCNU) and lomustine (CCNU), often in combination with simultaneous or sequential radiation, has led to median survival of 6–9 months [4, 7, 12–14, 16, 17, 23].

In a paper published 2 years ago, we reported a 25% CR rate and a 46% PR rate obtained in patients with brain

Table 1. Patient characteristics

Number of patients	61
Median age (range)	49 (30–67) years
Time between diagnosis of primary tumour and brain metastases (range)	38 (3–144) months
Median performance score (range)	1 (0–2)
Multiple metastases	82%

Table 2. Simultaneous radio- and chemotherapy protocol

Days	1	2	3	4	5	6	7	8	9	10
RT	X	X	X	X	X	X	X	X	X	X
IFO			X	X	X	X	X			
BCNU			X		X		X			
Dex.	X	X	X	X	X	X	X	X	X	X

RT, radiotherapy (1.5 Gy/day); IFO, ifosfamide (2 g/m^2); BCNU, carmustine (30 mg/m^2); Dex., dexamethasone (1.5 mg minimal dose)
Therapy-free interval, 4 weeks (three treatment courses scheduled)

metastases of different primary tumours using a combination of radiation and chemotherapy with ifosfamide and BCNU [15, 21]. A total of 38 breast cancer patients had an overall response rate of 71% and a mean survival of 10.9 months [15, 21]. In the present paper, the response and toxicity evaluation of 61 breast cancer patients treated with this combined modality regimen during the last 5 years is presented.

Patients and methods

Between January 1983 and April 1989, 61 patients with brain metastases of primary breast cancer were treated in the Robert Janker Clinic (Table 1). The data of these patients were evaluated retrospectively. The median age of all patients was 49 years, with a range of 30–67 years.

The average time between the diagnosis of the primary tumour and the cerebral metastases was 38 (range, 3–144) months. In 82%, multiple lesions were diagnosed by CT scan; these data correspond to those reported by others [8]. In all, 55.7% (n = 34) were premenopausal and 44.3% (n = 27), postmenopausal. Estrogen receptors were positive in 19.7%, negative in 45.9% and unknown in 34.4% Progesterone receptors were positive in 11.5%, negative in 54.1% and unknown in 34.4% of cases. All patients had been pretreated with surgery; 79%, with radiation; 64%, with hormones; and 74%, with chemotherapy for their primary tumour or for metastatic lesions elsewhere than in the brain. Most patients (i.e. 90.1%) were not only affected by brain metastases, but also suffered from involvement of other organs, especially the lung, bone or liver; 17 patients (27.8%) had metastases in three or more organs.

All patients received concurrent radio- and chemotherapy (Table 2). Radiation was carried out with cobalt 60. Using laterally opposing fields, the whole brain was irradiated in daily fractions of 1.5 Gy, for up to 15 Gy/treatment course. Three treatment courses were planned for all patients, such that the total radiation dose to the brain was 45 Gy.

The following chemotherapeutic protocol was given simultaneously with the radiation (Table 2): on 5 consecutive days, all patients received i.v. ifosfamide at a daily dose of 2 g/m^2 body surface. On the 3rd, 5th and 7th day of the treatment course, BCNU was given i.v. at a daily dose of 30 mg/m^2. After a therapy-free interval of 4 weeks, the treatment course was repeated. In all, 21.3% of the patients received one course of chemotherapy; 36.1%, two courses; and 32.7%, three courses. All of these patients (90.1%) received the total radiation dose of 45 Gy; 9.9% did not accomplish the first treatment cycle and were not amenable to statistical evaluation. To prevent radiogenic brain edema, all patients received a daily dose of at least 1.5 mg oral dexamethasone. If patients suffered from brain pressure due to tumour-induced edema, higher doses of 4–16 mg were given.

Table 3. Rates of remission

	Patients	%
CR	11	20.0
PR	25	45.4
MR	11	20.0
NC	4	7.3
PD	4	7.3
Evaluable	55	100.0

Table 4. Duration of remission in months

	Average	Median
CR	11.3	6.5
PR	8.1	6.0
MR	3.5	3.0
NC	3.8	3.0
Overall	7.8	5.5

Table 5. Survival in months

	Average	Median
CR	15.1	12.0
PR	11.8	10.0
MR	6.5	5.5
NC	6.7	5.5
PD	2.8	2.5
Overall	10.7	8.0

Results

To evaluate the effect of the treatment, the criteria of the International Union Against Cancer (UICC) for a complete (CR) and partial response (PR), no change (NC) and progressive disease (PD) were applied in the analysis of cranial CT scans [26]. Patients with clinical improvement, i.e. a reduction in neurological symptoms, but with <50% tumour reduction according to the CT scan, were classified as having shown a minor response (MR). This renders our results comparable with earlier studies by other authors, who often judged the therapeutic effect by the reduction in clinical symptoms instead of the size of the metastases.

After the therapy, 11 patients (20%) showed a CR; a PR was achieved in 25 patients (45.4%). In another 11 cases an MR was observed (20%). Overall, 7.3% of the patients showed NCs and 4 patients experienced PD (7.3%) (Table 3). The mean duration of the remissions was 7.8 (median, 5.5) months and depended on the quality of tumour response (Table 4). The mean duration of CRs was 11.3 (median, 6.5) months; that of PRs, 8.1 (median, 6) months and that of MRs and NCs, 3.7 (median, 3) months. The average survival was 11 months for all treated patients (median, 8 months) (Table 5). The mean survival of patients showing a CR was 15.1 (median, 12) months and that of those demonstrating an PR, 11.8 (median, 10)

months, whereas patients showing an MR or NC only survived 6.7 (median, 5.5) months. Patients with PD died in <3 months. It is noteworthy that in only 56.5% of the patients death was caused by a progression of the brain metastases; in 43.5%, the cerebral metastases remained in remission until death.

Side effects

The tolerance of the combined modality treatment was generally good. Most patients suffered from nausea and vomiting. Complete and permanent alopecia due to irradiation of the skull was observed in all patients, as was marked bone marrow depression. One patient died of acute gastro-intestinal bleeding due to long-term dexamethasone treatment; no other gastro-intestinal complications occurred. All changes in haematological parameters were reversible. No severe complications that might have been caused by the simultaneous application of radio- and chemotherapy were observed.

Discussion and Conclusions

According to the results of this retrospective analysis, the simultaneous combination of radiation and chemotherapy with ifosfamide and BCNU is a safe modality for the treatment of breast cancer patients with cerebral metastases and achieved encouraging results, confirming the preliminary data of our previous studies [15, 21].

In two large studies by the Radiation Therapy Oncology Group (RTOG), a median overall survival of 21 weeks was reported for breast cancer patients [2]; the use of hypoxic cell sensitizers could not improve these results [11]. The overall median survival obtained in the present study was 8 months. Patients showing a CR after radiation are known to have a median survival of approx. 6 months [9]. After radio- and chemotherapy on the present regimen, their median survival was 12 months. As serial CT scans were not carried out in the RTOG trials, it is difficult to compare these response rates. The reported overall response of neurological symptoms was 70%–80% [9], whereas the overall objective response rate (CRs, PRs, MRs) in our study was 95%. With chemotherapy alone, the response rate of breast cancer with brain metastases is only 10% [24].

Thus, both the rates and the duration of tumour response seem to be higher after combined radio- and chemotherapy than after the exclusive use of either radiation or chemotherapy. However, the superiority of the combined modality treatment can be proven only in a prospective randomised trial. The toxicity of the combination treatment was moderate; no severe gastro-intestinal or haematological complications that could have been caused by the simultaneous application of radiation and chemotherapy were observed.

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