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Palliative chemo-radiotherapy with ifosfamide and epirubicin as first-line treatment for high-risk metastatic breast cancer*

Results of a prospective multicenter trial

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Summary. From June 1986 to December 1988, 107 patients (median age, 49 years; median performance score, 1) with haematogeneous metastases from breast carcinoma were treated with concomitant radiation and chemotherapy. Overall, 97% of the patients had been pretreated with surgery; 65%, with radiation; and 56%, with hormones. In all, 38% had received adjuvant chemotherapy. Patients with prior palliative chemotherapy were excluded from the study. All patients fulfilled at least two high-risk criteria. Chemotherapy was given according to the EI protocol (4-epirubicin and ifosfamide), and all patients simultaneously received radiation to the main tumour sites. Gastro-intestinal toxicity was moderate (11.1%, WHO grade 4), and bone marrow depression was marked in all cases. After three treatment courses, the overall response rate was 67% [21% complete response (CR), 46% partial response (PR)]. In all, 28% had stable disease (NC) and the rate of progressive disease (PD) was 5%. The median duration of tumour response was 8 months, with 12 months for CRs, 9 months for PRs and 6 months for NCs. The median survival was 13.5 months.

Introduction

In spite of the improvements that have been made in surgical, radio-therapeutic and (neo-)adjuvant chemotherapeutic management of breast cancer, the definitive overall cure rate is still <35%, depending mainly on the primary stage of disease [3]; therefore, palliative treatment modalities are most important [21]. Because of the extremely different courses of the various types of breast cancer, the palliative treatment of metastatic disease has been controversial over the last decade. On the one hand, aggressive high-dose chemotherapy has been recommended, and on the other, less toxic and less effective substances have been used in recent years so as not to compromise the quality of life of incurably ill patients. The need for a more individual mode of therapy is unanimously accepted. Maximal palliation should be achieved with a minimum of treatment-related toxicity [2]. In patients with poor prognosis factors, e.g. rapidly growing tumours and/or visceral organs as the major sites of metastases, high-dose cytotoxic treatment remains inevitable [24]; in these patients, the quality of the first remission is of great prognostic impact [24].

The fear of treatment-related, reversible side effects should not outweigh the hope to achieve long-term palliation of tumour-related symptoms. In the long run, improvement of the quality of life of these high-risk patients can be attained only by the induction of a tumour remission, at the cost of a certain treatment-induced toxicity [16]. To improve the results, several attempts have been made during the last 10 years. Thus far, however, the use of more than two or three chemotherapeutic drugs, their combination with hormones, alteration of the doses or the introduction of new compounds have not been able to improve the results significantly [10, 17]. Using regimens that contain Adriamycin and cyclophosphamide as the most active single agents in metastatic breast cancer [12, 25], the achievable overall response rates are 40%–70% [2, 9, 22]. The overall survival of approximately 15 months has not changed significantly in recent years [9].

To overcome this stagnation, high-dose regimens and combined modality treatments may be useful. A number of experimental and clinical data suggest that improved chemotherapeutic results may be obtained by increasing the drug dose intensity (mg drug/m^2 per week) [8, 13, 16]. It is also well known that the efficacy of alkylating agents depends on the amount of the single dose more than on the total dose given in a fractionated schedule. The cumulative toxicity and the development of tumour cell resistance are less pronounced if the drugs are given at high doses over a short period of time [4, 6, 11].

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Table 1. High-risk criteria

Factor	Patients
Premenopause	45.9%
Negative or unknown ER	68.0%
Negative or unknown PR	74.0%
Disease-free interval of <2 years	61.5%
Visceral metastases	70.8%

ER, estrogen receptors; PR, progesterone receptors

Table 2. Treatment undergone prior to the present study

Treatment	Yes	No
Surgery	104 (97.2%)	3 (2.8%)
Radiation	69 (64.5%)	38 (35.5%)
Hormones	60 (56.1%)	47 (43.9%)
Chemotherapy (adjuvant)	41 (38.3%)	66 (61.7%)

Table 3. Extent of disease

Number of metastatic sites	Patients (*n*)
1	27
2	35
3	24
⩾4	13

Table 4. Chemotherapy regimen

Days	Drugs	Single dose	Total dose
1, 2	4-epirubicin	30 mg/m^2	60 mg/m^2
3–7	ifosfamide	60 mg/kg	300 mg/kg
3–7	mesna	12 mg/kg (× 3)	180 mg/kg

As simultaneous radiation and chemotherapy has proved to be effective in a number of malignant solid tumours [1, 7, 11, 15, 18–20, 26], this concept seems to be worth studying in metastatic breast cancer as well. A pilot study published in 1985 achieved an overall response rate of 87%, with 16% complete response (CR), in patients with metastatic breast cancer by using the newer drugs ifosfamide and epirubicin concomitantly with radiation to the main tumour sites [14]. This modified Adriamycin-cyclophosphamide (AC) regimen (EI) was well tolerated, because epirubicin is less cardiotoxic than Adriamycin and ifosfamide causes lower cumulative toxicity than cyclophosphamide [5, 14, 22]. The present study was initiated in May 1986 to see if the encouraging results of the previous retrospective analysis could be confirmed in a prospective trial.

Patients and methods

Patients. From June 1986 until December 1988, 107 patients with metastatic breast cancer entered the study. Selection critera included progressive metastatic breast cancer with measurable disease, an age of <70 years, a WHO performance status of 0–2, life expectancy of >3 months, more than two poor-prognosis criteria, no brain metastases, no significant bone marrow depression, bilirubin values of <2 ml/dl, creatinine levels of <1.5 ml/dl and no prior palliative chemotherapy. In all, 99 patients completed the therapy, 94 of whom were evaluable for tumour response. The median age was 49 years (range, 25–66 years), and the median performance score was 1 (range, 0–2).

High-risk factors (Table 1) included the following: 45.9% of the patients were premenopausal; 32% had negative and 36%, unknown, estrogen receptors; progesterone receptors were negative in 36% and unknown in 38%; >60% of the patients had a disease-free interval lasting <2 years; and in more than two-thirds of the cases, visceral organs were the primary sites of metastases.

In all 104/107 patients (97.2%) had previously been treated with surgery and 69/107 (64.5%), with radiation; 60/107 (56.1%) had received one or more hormonal manipulations; adjuvant chemotherapy had been given in 41/107 (38.3%) (Table 2).

The extent of disease in our patients is shown in Table 3. Overall, 37/99 patients (38%) had metastases in three or more organs. One organ was affected in 27 cases, and in 35 patients two organs were involved by the disease. In accordance with internationally published papers, the main sites of metastases were the skeleton (50 cases), the lung (36 cases) and the liver (34 cases). In all, 46% of our patients had a mixed type of metastatic spread (i.e. visceral and bone or lymph node metastases), 20% had only visceral involvement and 34%, only bone or locoregional metastases.

Methods. Radiation was carried out with cobalt 60, electrons and photons of a linear accelerator or 300 kV X-rays using a standard fractionation (1.2–2 Gy, 5 times/week) and varied from 40 to 60 Gy for bone, lung and soft-tissue metastases. The radiation dose was given by a split-course regimen, and radiation courses were given simultaneously with chemotherapeutic cycles.

In patients with multiple lesions in the lung or liver, large treatment volumes were irradiated with single doses of 1 Gy, up to a total dose/treatment cycle of only 6 Gy. Chemotherapy consisted of 30 mg/m^2 4-epirubicin on the first 2 days. On days 3–7 patients were given 60 mg/kg ifosfamide followed by mesna rescue (3 × 12 mg/kg) to prevent hemorrhagic cystitis (Table 4). After a therapy-free interval of 4–5 weeks, this high-dose regimen was repeated; a total of three courses was scheduled. The median cumulative dose of epirubicin was 265 mg/patient.

The median duration of treatment was 2.8 months (range, 1–4 months) and depended on the number of treatment courses. All 94 patients completed the first cycle, 85/94 (90.4%) finished the second cycle and 63/94 (67.0%) completed the third cycle of the combined modality treatment. A total of nine patients discontinued therapy after the first course, seven because of progressive disease and two due to refusal of treatment. In all, 22 patients went off-study after the second course, 7 because of PD, 7 due to refusal of treatment and 8 because a CR or PR had been achieved by that time.

Results

Response was evaluated after each course of treatment. The rate of CR was 1.1% after the first treatment course and 20.6% after the third. The rate of PR was 42.6% after the first cycle and 46% after the third. The percentage of NC was 48.9% after the first course and 28.6% after the third. In all, 7.4% of the patients experienced PD after the first course; 8%, after the second; and 5%, after the third.

Table 5. Response rate in different metastatic sites

Localisation	CR (%)	PR (%)	NC (%)	PD (%)
Bone	0	43.3	56.7	0
Liver	13.0	52.2	26.1	8.7
Skin	38.9	33.3	22.2	5.6
Lung	45.8	33.3	16.7	4.2
Lymph node/soft tissue	52.7	34.2	10.5	2.6

Table 6. Median duration of remission

Overall	8 months
CR	12 months
PR	9 months
NC	6 months

Patients with PD discontinued the study and received a second-line chemotherapeutic regimen.

Among all 94 patients there were 13 CRs (13.8%), 43 PRs (45.8%), 21 NCs (22.3%) and 17 PDs (18.1%). Among the 63 patients who completed the three courses of chemo- and radiotherapy, there were 13 CRs (20.6%), 29 PRs (46.0%), 18 NCs (28.6%) and 3 PDs (4.8%), for an overall response rate of 66.6%.

It is important to stress that more than half of the patients ($n = 50$) were affected by (apart from other metastases) involvement of the skeleton, which presents difficulties for an assessment of response evaluation, as is well known. When the response rates were evaluated separately for the various sites of metastases, there were some significant differences (Table 5). In bone metastases no CRs and only 43.3% PRs were seen, whereas the rate of NCs was 56.7%. In contrast, the overall response rates for other involved organs varied from 65.2% (liver), to 72.2% (skin), to 79.1% (lung) and, finally, to 86.9% (lymph node and soft-tissue metastases). Most interesting was the 46% CR rate for patients with lung metastases. The overall median duration of tumour response was 8 months, with a range of 1–28 months, depending on the quality of the remission (Table 6). The median duration of CRs was 12 months; that of PRs, 9 months; and that of NCs 6 months. The median survival was 13.5 (2–31) months. Patients showing a CR or PR lived significantly longer than non-responding patients.

Side effects

Overall toxicity was moderate. All patients suffered from WHO grade 2 nausea; 17/94 (18.1%) had WHO grade 3 nausea and vomiting and 11/94 (11.7%), WHO grade 4. Due to antiemetic treatment, vomiting episodes number less than five per day in all cases. No grade 3 or 4 mucositis or stomatitis was seen. In all patients, complete, reversible alopecia (WHO grade 3) was observed, as was marked but reversible leucopenia (WHO grade 4) with a nadir of 300–1,000 (median, 700) WBC/mm^3. Due to prophylactic antibiotics (doxycyline, 100 mg/day) and desinfection of the oral cavity, only 13/94 patients (13.8%) developed feverish infections during bone marrow depression and therefore required i.v. antibiotics. There was one treatment-related death. Reversible grade 3 thrombopenia was observed in 32% of the patients.

Due to prolonged bone marrow depression, treatment was delayed in three cases after the first and second therapy courses. There was no increased rate of radiogenic erythema or fibrosis that could have been caused by the simultaneous application of radio- and chemotherapy. No clinically relevant cardiotoxicity was observed.

Discussion

For high-risk breast cancer patients, apart from survival data, the response rates and the median time to progression are the most important end points. In our study, the simultaneous combination of radiation to the main tumour sites and chemotherapy with ifosfamide and epirubicin achieved relatively high overall response rates in patients with advanced haematogeneous metastases (CRs 21%; PRs 46%). However, the extremely encouraging response rates (CRs and PRs 87%) of the previous pilot study, which was evaluated retrospectively, could not be reproduced [13, 14]. This is most probably due to the high percentage of patients with bone metastases in whom, as is well known, CRs or PRs are not very common and are difficult to evaluate when the strict criteria of the UICC are applied [17]; thus, no CRs and only 43% PRs were seen in patients with bone metastases.

In contrast, the response rates of patients with visceral metastases seemed to be superior to the published results achieved by chemotherapy alone. The highest commonly accepted overall response rate in breast cancer with haematogeneous metastases has not exceeded 75% and has been achieved by anthracycline-containing regimens such as AC, VAC, FEC and others [2, 9, 22]. A recent study using high-dose epirubicin and cyclophosphamide reported a 78% response rate, with 37.5% CRs for patients with visceral metastases [17]. The similarly good response of our patients with metastases elsewhere than in the bone, especially those with lung (CRs and PRs, 79%) and soft-tissue metastases (CRs and PRs, 87%), may have been caused by the relatively high doses of ifosfamide (total dose, approximately 12 g/m^2) and/or by the additional positive interactions with radiation.

Besides the so-called spatial cooperation and independent cell kill, both of which are well-known effects of combined radio- and chemotherapy, a number of experimental and clinical data support the hypothesis of an enhancement of tumour response by potentiation of the efficacy of radiation and chemotherapy [23]. In the present study, the median duration of tumour response was 8 months. The average duration of CRs (12 months) was longer than that of PRs (9 months) or NCs (6 months). These results are in accordance with those obtained in most other chemotherapy trials in metastatic breast cancer [2, 9, 22].

It is important to stress that in no case were more than three treatment courses given, the result being that the duration of treatment never exceeded 4 months. The median duration of treatment was only 2.8 months. This

means that, in contrast to other studies, the period of time spent in remission and off chemotherapy was relatively long for many patients, a fact that is important for their quality of life.

The side effects of the combined modality treatment were moderate. No clinically relevant cardiotoxicity was observed. Marked leucopenia was seen in all patients (WHO grade 4), 14% of whom developed feverish infections during bone marrow depression. There was one treatment-related death. In contrast to results reported in other publications, in the present study there was no increased rate of radiogenic erythema or fibrosis due to the concomitant chemoradiotherapy, although an anthracycline derivative was used. Because of the encouraging results in high-risk patients with visceral metastases, combined radio- and chemotherapy with ifosfamide and epirubicin may be considered as first-line treatment for this sub-group of patients. Due to the high response of patients with visceral metastases to the high-dose EC regimen [16, 17], a new trial using an increased dose of epirubicin (100 mg/m^2) has been started in an attempt to improve the results. If the problem of the relatively short duration of remissions can be overcome by low-dose maintenance therapy with epirubicin, this question should be studied in a prospective randomised trial.

References

1. Ammon J, Karstens JH, Katsholi D (1988) Simultane Strahlen- und Chemotherapie beim Schilddrüsenkarzinom. Tumor diagn Ther 9, [Sonderh]: 18–20
2. Bartels H (1985) Chemotherapie beim Mammakarzinom. In: Schildberg FW, Kiffner E (eds) Interdisziplinäre Therapie des Mammakarzinoms. Perimed, Erlangen, pp 214–220
3. Bastert G (1983) Aktueller Stand der Therapie des Mamma-Karzinoms. Therapiewoche 33: 6747
4. Blumenberg FW, Scheef W (1969) Hochdosierte Cyclophosphamid-Behandlung in Kombination mit Strahlentherapie bei Patienten mit fortgeschrittenen Tumorerkrankungen. Med Welt 20: 2024
5. Brock N, Hoefer-Janker H, Hohorst HJ, Scheef W, Schneider B, Wolf HC (1973) Die Aktivierung von Ifosfamid an Mensch und Tier. Arzneim-Forsch 23: 1
6. Druckrey H, Steinhoff W, Nakayama M, Preussmann R, Anger K (1963) Experimentelle Beiträge zum Dosis-Problem in der Krebs-Chemotherapy und zur Wirkungsweise von Endoxan. Dtsch Med Wochenschr 88: 651
7. Dühmke E (1984) Cisplatin und Radiotherpaie. Zentralbl Radiol 128: 133
8. Frei E III, Canelos GP (1980) Dose: a critical factor in cancer chemotherapy. Am J Med 69: 585–594
9. Fritze D (1986) Medikamentöse Krebsbehandlung. Steinkopf, Darmstadt, pp 284–293
10. Harris JR, Hellmann S, Canellos GP, Fisher B (1985) Cancer of the breast. In: De Vita VT, Hellmann S, Rosenberg SA (eds) Cancer. Principles and practice of oncology. Lippencott, Philadelphia, pp 1119–1177
11. Hoefer-Janker H, Scheef W (1973) Kombinierte radiologisch-zytostatische Behandlung mit Ifosfamid bei generalisierten malignen Hodentumoren. Röntgen Ber 2: 186
12. Hoogstraaten B, Fabian C (1979) A reappraisel of single drugs in advanced breast cancer. Cancer Clin Trials 2: 101–109
13. Hryniuk W, Bush H (1984) The importance of dose intensity in chemotherapy of metastatic breast cancer. J Clin Oncol 11: 1281
14. Lange OF (1987) Behandlung des fortgeschrittenen metastasierten Mammakarzinoms. MMW 129: 361–364
15. Lange OF, Schlechtingen J, Heckmann M, Abresch HL (1985) Kombinierte Strahlen- und zytostatische Chemotherapie primär inoperabler und rezidivierender maligner Tumoren im HNO-Bereich. Tumordiagn Ther 6: 234–237
16. Nagel GA, Beyer HJ, Holtkamp W, Emrich D, Kneba M, Luig H, Marschner N, Rauschning W, Unger C, Wander HE (1988) High-dose epirubicin + cyclophosphamide (HD-EC) in metastatic breast cancer: a dose finding study. Short communication. Onkologie 11: 287–288
17. Nagel GA, Rauschning W, Ammon A, Beyer JH, Emrich D, Holtkamp W, Kneba M, Luig H, Marschner N, Unger C (1988) High-Dose epirubicin + cyclophosphamide (HD-EC) in metastatic breast cancer: preliminary data of a phase II study. Short communication. Oncologie 11: 289–291
18. Pape H, Zamboglou N, Fürst G, Schmitt G (1988) Simultane Strahlen- und Chemotherapie bei undifferenzierten Weichteilsarkomen. Tumordiagn Ther 9: [Sonderh]: 31–34
19. Schmitt G, Arndt D, Hossfeldt KD (1984) Kombinierte Therapie bei Tumoren des Erwachsenen. Zentralbl Radiol 128: 133
20. Schmitt G, Heuser L, Schmidt C (1984) Bestrahlung, Cis-Platin-Sensibilisierung und Operation bei der Behandlung fortgeschrittener Kopf-Halstumoren. Zentralbl Radiol 128: 134
21. Schmoll HJ, Fink U (1987) Mammakarzinom. In: Schmoll HJ, Peters HD, Fink U (eds) Kompendium internistischer Onkologie, Teil 2. Springer, Berlin, p 1240
22. Seeber S (1985) Chemotherapieresistenz beim Mammakarzinom. In: Herfarth CH, Betzler M (eds) Das Mammakarzinom. Karger, Basel, pp 102–111 (Beiträge zur Onkologie)
23. Steel GG (1984) Radiotherapy/chemotherapy interactions. Zentralbl Radiol 128: 131
24. Wander HE, Nagel GA (1986) Mammakarzinome 4. Zuckschwerdt, München
25. Salmon SE, Jones SE (1979) Untersuchungen der Kombination Adriamycin und Cyclophosphamid (allein oder mit anderen Substanzen) zur Behandlung des Mammakarzinoms. Onkologie Sonderdruck 2
26. Zamboglou N, Schmidt C, Pape H, Fürst G, Schmitt G (1988) Aspekte der kombinierten Radio- und Chemotherapie bei fortgeschrittenen Kopf-Hals-Tumoren. Tumordiagn Ther 9 [Sonderh]b35–40
27. WHO (1979) Handbook for reporting results of cancer treatment. WHO Offset Publication 48. World Health Organisation, Geneva