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No relevant influence on overall survival time in patients with metastatic breast cancer undergoing combination chemotherapy *

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Summary. The results of clinical studies dealing with first and second line chemotherapy of metastatic breast cancer published between 1975 and early 1986 which involved 9350 women were reviewed. Our special aim was to evaluate combination chemotherapy and its influence on overall survival in late stage breast cancer patients. No significant improvement in overall survival times was found in this selected group of patients who were treated with intense palliative chemotherapy.

Key words: Cytotoxic chemotherapy – First line – Second line – Metastatic breast cancer – Overall survival

Introduction

During the last year, extensive analyses of results obtained in clinical studies on the therapeutic efficacy of cytostatic treatment in patients with metastatic breast cancer were carried out. Our retrospective reviews [5, 6], which compiled results from first line combination chemotherapy and second line treatment with various single agents or combination regimens, involved 9350 patients (6500 first line, 2850 second line). It was intended to objectively evaluate the role of intense combination chemotherapy in late stage breast cancer. For this purpose the most important therapeutic parameters such as mean remission rates, duration of remission, and mean survival time were examined for the most common chemotherapeutic modalities. Our special aim was to investigate whether the mean survival time of patients with metastatic breast cancer treated between 1975 and early 1986 was improved.

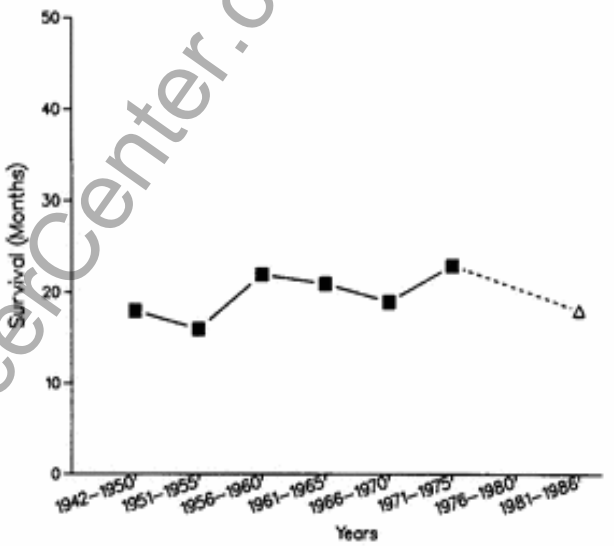

Fig. 1. Median metastatic survival time of patients treated with first line combination chemotherapy (analysis concerning therapeutic results published between 1975 and 1986 in comparison to previous findings by Patel et al. [4]). ■ Patel et al. (1985); △ Petru and Schmähl (1986, 1987)

The group reviewed was a select group of patients subjected to intense drug therapy and findings were compared with previous results reported by Patel et al. [4] (Fig. 1). In Patel's study the median metastatic survival time of an unselected cohort of patients during several periods between 1942 and 1975 was examined. The authors concluded that in spite of a steady increase in the proportion of patients treated by chemotherapy and/or hormonal therapy the survival time from first recurrence did not increase in these patients during the period of the study.

Materials and methods

All patients included in studies published between 1975 and early 1986 and who had proven metastatic disease and received first or second line chemotherapy were reviewed. Approximately 40 different

* Dedicated to Professor Dr. med. Dr. med. h.c. (mult.) F. Linder, Heidelberg on the occasion of his 75th birthday

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Table 1. Therapeutic results achieved with combination chemotherapy in metastatic breast cancer (mean values)

	Complete remission (%)	Partial remission (%)	Duration of remission (months)	Overall[a] survival times (months)
First line	10–20	30–50	10	18
Second line	0–10	20–40	6	10

[a] From start of therapy

regimens of combination therapy were used worldwide in the first line, whereas more than 50 schedules or single agents were used as a second line treatment. Most of the therapeutic regimens were composed of cyclophosphamide, adriamycin, 5-fluorouracil, methotrexate, or vincristine in various combinations (e.g., CAF, CMF, AV/CMF, AC, CAMF). The mean values of remission rate (complete and partial remission), duration of remission, and overall survival time were based on results obtained from different clinical studies in which patients received drug combinations or single agents. The total number of patients treated with the same schedule or monotherapy was recorded. The data were categorized on the basis of quantity. This led to different classifications for first line cytotoxic combinations i.e., under or above 200 patients and for second line combination regimes or monotherapy i.e., 50 patients or less. Results based on larger numbers of patients are of more indicative value than findings based on lower numbers. There was also no evidence that therapeutic efficacy of first and second line chemotherapy differed significantly in studies involving less than 200 or 50 patients. The present compilation considers results which were established in larger cohorts only. This applied to 11 combination regimens (first line) and 21 second line drug therapy modalities.

Results

Mean remission rate, mean duration of remission, and mean survival time calculated in our previous papers [5, 6] are summarized in Table 1. Although the combinations used were composed of cytotoxic agents with alleged different mechanisms of action, e.g., alkylating agents, antimetabolites, antimitotics, ferments, or intercalating agents, no relevent differences were observed with regard to their therapeutic efficacy and side effects. Analysis of response by site of metastatic lesion [6] revealed favorable response rates in lesions of the soft tissue and lymph nodes (~70%) compared with the lung (~50%), liver (~35%), and bone (25%).

Discussion

The results indicate that the approach of therapeutically exploiting the different pharmacodynamics of cytotoxic drugs in combination schedules did not meet the expectations, i.e., the achievement of an additive synergism in cases of late stage breast cancer. The present analysis concludes that not even the most aggressive measures in palliative treatment could favorably influence the average survival time of patients included in the respective clinical trials. We think that from the ethical point of view it seems problematic to apply aggressive chemotherapy programs to patients with metastatic disease, since no significant therapeutic effect in terms of prolongation of life-span can be assumed. Although the prolonged life in late stage breast cancer patients responding to chemotherapy is well-established and the beneficial effect of a temporary remission on the well-being of a patient who can put her affairs in order cannot be disregarded, it must be remembered that nonresponding patients are exposed to side effects associated with this kind of therapy without profiting from it. Therapeutically active combination regimens which exhibit a tolerable degree of adverse effects are urgently needed especially for the treatment of late stage breast carcinoma. When considering the differences of therapeutic parameters caused by genetic resistance between first and second line chemotherapy, widely used adjuvant therapy may have a negative influence on the efficacy of cytotoxic chemotherapy in metastatic disease. When evaluating large cohorts of patients, the individual case remains unconsidered even though that person may have a better response than the mean value suggests.

Primary aggressive polychemotherapy seems to be indicated only if a patient shows unfavorably prognostic factors such as negative hormone receptor status, locally recurrent carcinoma, or fulminant progressive disease with metastases in the liver or brain. Of course the palliative use of this type of therapy is unquestionable for the treatment of the patient's pain.

The frustrating therapeutic results obtained with combination chemotherapy underline the need for early detection and early active treatment of breast carcinoma. Intensive research on the development of new classes of antineoplastic compounds is essential. Further efforts are warranted especially in this field in order to have a realistic chance of improving the life expectancy of patients with metastatic breast cancer; for instance, if the promising therapeutic efficacy of hormone-linked cytostatics, alkylphosphocholines, 4-amino-*N*-(2'-aminophenyl)-benzamide or razoxane observed in preclinical studies [1–3, 7] is confirmed in humans, these compounds may possibly take the place of today's conventional chemotherapy programs in the future.

References

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