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REVIEW ARTICLE

CHEMOTHERAPY IN ADVANCED BREAST CANCER

S. GUNDERSEN and S. KVINNSLAND

Therapy with cytotoxic drugs in advanced breast cancer is a subject of controversy. A comprehensive literature reporting numerous chemotherapy regimes with wide variation in response rates and toxicity can cause confusion for the clinician. Extensive and objective reviews are difficult to write and are of value only if they attempt to draw reasonable conclusions and provide simple general guidelines. This review will not give detailed analyses of every single contribution, but put emphasis on possible response rate, duration of response, influence on survival, toxicity, and patient selection. The most commonly used chemotherapy regimes will be discussed and guidelines according to the views of the authors will be given.

Therapeutic goal

Although a large number of patients with advanced breast cancer have been treated with chemotherapy, no patients have ever been cured by such treatment. Furthermore, the use of chemotherapy has not uniformly given a survival benefit from the time of first metastasis (55, 58, 65). Accordingly, the major aim of chemotherapy in advanced breast cancer is palliation.

In practical terms, palliation means that toxicity from treatment should be more than compensated for by relief from tumor symptoms. In other words, treatment should hit the tumor harder than the patient. On the other hand, it has been claimed that response to therapy is more important in determining the quality of the patient's life than the toxicities of the actual therapy (5).

Response rate

Tumor regression is expressed as various degrees of response according to certain criteria (35, 50). The number of patients obtaining remission divided by the number of patients treated is called the response rate (RR). The RR represents a score for efficacy of a given treatment. It is therefore pertinent first to discuss which RR can be expected. The RR may vary from 20 to 70 per cent (15) for identical regimens. Besides pure random variations, this reflects the heterogeneity of breast cancer populations and also to some degree variations with regard to evaluation. The characteristics of a patient population depend on the selection of the patients for the study. In publications and presentations, patient characteristics therefore must be carefully evaluated.

Performance status as expressed in ECOG (50) or as the Karnofsky index (41) has been shown to have a major impact on RR (67). Pretreatment performance status often correlated very well to the extent of metastatic spread, i.e. the tumor burden.

Tumor burden. Time from first metastatis until start of treatment might influence RR. When chemotherapy is administered to a group of patients as primary metastatic treatment irrespective of estrogen receptor status, an RR of approximately 50 per cent has been reported (8, 36), while we found an RR among hormone resistant patients of approximately 35 per cent (33). The influence of various sites of the metastasis with respect to response to chemotherapy has been analyzed. Rather small differences were found, suggesting that the tumor burden is more important than the site of involvement (64). The attitude of the physician towards chemotherapy might influence the time period from first metastasis until start of treatment. Some start treatment at the time of the first small local recurrence, stating that this is a certain sign of disseminated disease. Others feel that since the patient cannot be cured, extirpation or irradiation should be preferred, for local palliation, and postpone chemotherapy until definite confirmation of disseminated disease has

From the Department of Medical Oncology and Radiation Therapy, The Norwegian Radium Hospital, Oslo, and the Department of Oncology, Haukeland Sykehus, Bergen, Norway.
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been obtained. In many departments hormonal treatment, being less toxic, is the primary choice in disseminated disease. Thus, the tumor burden, and thereby the possibility of obtaining an objective response will vary considerably in the patient population of different studies.

Previous treatment with chemotherapy reduces the possibility of response (64). This has the serious implication that a new, potentially useful drug may be erroneously rejected. Cis-platinum, for instance, was originally (13, 28, 72) reported to have minimal therapeutic activity until KOLARIC & ROTH (45) found considerable response in previously untreated patients. A low RR is also seen in previously irradiated patients (31, 40), especially of metastases within the irradiated volumes.

Evaluability of lesions might also influence RR. Likewise, skeletal metastases in some studies (2, 61) have been reported to respond poorly. The evaluability of such lesions, as stated in a protocol, will therefore influence the RR. In a study by the Southwestern Cancer Study Group (60) comparing two chemotherapy regimes, RR for the best regimen was 64 per cent. Patients with only bone metastases, however, were not randomized, although included. The RR for these patients was 11 per cent. If they had been randomized, this would have resulted in a decrease in RR for the best treatment from 64 to 52 per cent.

Other criteria of selection. Rapidly progressing disease reflects an aggressive biologic behaviour, but often also lack of treatment efficacy. Nevertheless, patients will often be excluded if they are expected to die within a few weeks after start of treatment. At least two courses of chemotherapy constitute another criterion for evaluation stated in some treatment protocols. This will select patients with a better prognosis.

Conclusions. RR does not always reflect the efficacy of chemotherapy in an unselected population, but is only representative for the patients who have met all requirements of a specific protocol. It is important to select patients who may profit from treatment. However, it is difficult to deny patients chemotherapy because they do not fulfil all protocol requirements. The possibility always exists that treatment for the individual patient may be of benefit. Generally, the RR in a population that is selected in randomized studies will be higher than in a series of patients treated consecutively. Thus it is quite conceivable that the RR for a given regime can vary considerably, depending upon selection criteria.

Duration of response

The response rate is often quoted with special emphasis, but the rate of complete responses and the duration of response might be of greater importance. In most published studies *complete responses* are seen among less than 20 per cent of the patients and for unselected cases in less than 10 per cent (7, 36). The *median duration* of partial and complete remissions is usually 6 to 8 months (7, 36), somewhat longer for complete remissions. Remissions lasting for more than 2 years are only occasionally seen. The duration will depend on the the strictness and frequency of response evaluation. In a retrospective study of 647 patients reported by FISCHER et coll. (27), only 4 per cent were considered to have had a complete remission. However, the median duration for these patients was 27.5 months.

It is important to point out that the definition of duration of a complete response, according to the UICC criteria (35), is calculated from start of treatment, while according to WHO criteria (50), the duration of a complete remission is calculated from the date of its recognition.

Survival

When considering survival figures, it is of importance to know whether calculations are made from first relapse or from start of treatment. At our institutions median survival from first relapse is 2 to 2½ years and almost all patients are dead within 5 years. When calculated from start of treatment, median survival in trials has been 11 to 12 months with 80 per cent of the patients dead within 24 months (33).

Chemotherapy can offer meaningful palliation, such as shrinking or even complete healing of ulcerated and malodorous lesions, and improvement of pulmonary function after incapacitation from lymphangitic spread, lung or pleural metastases. Sometimes, reduction or even alleviation of pain due to skeletal metastases may occur, and symptomatic and objective improvement of liver disease and other abdominal manifestations may be seen. Based on clincal experience in individual cases, especially when viscera are involved, the impression is gained that life has been prolonged. The impact of chemotherapy on survival for a larger group of patients, however, is less clear. POWLES et coll. (58) failed to demonstrate improvement in overall survival of patients over a ten year period despite increased use of multiple drug chemotherapy. PATERSON et coll. (56) found that patients treated from 1975 to 1978, when management policies favoured aggressive combination chemotherapy, only had a minor benefit in overall survival when compared with patients treated from 1971 to 1974, when single agent sequential regimes were mainly used. In a study published by CHLEBOWSKI et coll. (21), there appeared to be no difference in survival between patients without liver involvement treated with a combination of drugs, or with single agents in sequence. These studies were all retrospective. Questions with regard to the effect of chemotherapy on survival can be adequately answered only by prospective randomized studies, where treated patients are compared with patients not treated with chemotherapy. However, anecdotal evidence of long lasting remissions seems to prevent such studies. Another option is to compare survival in randomized studies where response rates between two treatment arms differ significantly. Several studies of this type have been published. CAVALLI et coll. (18) found significantly longer survival

after more aggressive chemotherapy than after a less toxic regimen, in a prospective randomized study. In another study, TORMEY et coll. (66) found that the survival of responders was the same regardless of the treatment used (single agent in sequence versus combinations in sequence). However, the median survival of all patients treated with combination chemotherapy was several months longer. KVALØY et coll. (43) showed that although two regimens differed significantly (18 versus 36%) with regard to RR, there was no difference in survival. In conclusion, until further prospective randomized studies have been undertaken, the impact of chemotherapy on survival of patients with advanced breast cancer remains uncertain.

Selection of patients and start of chemotherapy

Since patients with breast cancer can respond to various forms of endocrine therapy, used sequentially, and with minimal toxicity, the possibility of response to such treatment should always be considered before chemotherapy is started. Likewise, since the impact of chemotherapy on survival remains uncertain the possibility of local treatment alone should be kept in mind. Skin relapses or regional lymph node metastases can in many cases be treated with surgery and/or radiation therapy. Tumors that are removed should be examined for steroid receptors. In receptor positive patients the policy in our institutions has been to give endocrine treatment (tamoxifen) in addition to the local therapy. For local relapses which are ER negative, the area involved, including the regional lymph nodes in ipsilateral local recurrences, will be irradiated and chemotherapy postponed. When local relapses are located within irradiated fields, chemotherapy will often be inefficient and surgery should be considered. Likewise, bone metastases often respond well to radiation therapy, resulting in relief from pain (59). When the disease cannot be controlled by local treatment, ER negative patients receive chemotherapy as first line treatment, i.e. before endocrine therapy. This is based on the observation that ER negative patients will respond to hormonal treatment in less than 10 per cent of cases (38, 49). However, hormonal treatment might be given later in the course of the disease. Liver metastases can be ER positive (46, 47). Nevertheless, the general experience is that response of liver metastases to endocrine therapy is rare. Rapidly evolving or extensive liver metastases are probably best treated with chemotherapy. In these cases expected survival time is generally limited. It might be preferable to give both chemotherapy and hormonal therapy to these patients.

Selection of the chemotherapy regimen

Among the established chemotherapeutic drugs, doxorubicin, cyclophosphamide, methotrexate, 5-fluorouracil, and mitomycin-C have been evaluated in phase III studies. The active drugs, 4-epidoxorubicin, mitoxantrone, and cis-platinum are under current investigation.

The concept of GOLDIE & COLDMAN (30) implies that tumor resistance to drugs is connected with specific cell cycle phases (G_0), presence in inaccessible sanctuary sites (e.g. CNS), or spontaneous mutations giving rise to resistant cells. They further emphasized that the number of resistant cells would be proportional to the number of tumor cells, i.e. a decrease in the chance of curability with increasing tumor burden. The Goldie-Coldman model also predicts pleiotropic resistance, which means that resistance obtained to one drug or family of drugs can be conferred to drugs with dissimilar mechanisms of action. The mechanisms behind the resistance to chemotherapy (54) and their clinical implications (74) have lateley been reviewed.

One of the most important concepts to be derived from the Goldie-Coldman model is that combination chemotherapy should be more effective than single agent therapy. In 1969, COOPER (22) introduced a combination chemotherapy which rapidly became a standard treatment because of the high RR described in the initial report. This regimen utilized cyclophosphamide (C), methotrexate (M), 5-FU (F), vincristine (V) and prednisone (P) (CMFVP). However, subsequent trials (1) using slight modifications of this regimen failed to confirm its reported efficacy. Randomized trials evaluating different combinations of these drugs have concluded that CMF or CMFP have the same efficacy as CMFVP but less toxicity. With the background of randomized trials the role of vincristine has been questioned (2, 12, 68). While the added therapeutic efficacy of vincristine is doubtful, it certainly adds considerable toxicity, especially neurotoxicity. Since the introduction of doxorubicin (Adriamycin), several combinations (VAC or FAC) have been evaluated. As with the Cooper regimen the role of vincristine (20, 63) is unclear. Multiple randomized trials have been designed to compare doxorubicin combinations with CMF, CMFP or CMFVP (4, 8, 12, 14, 24, 52, 60). There seems to be a trend for combinations containing doxorubicin to have a somewhat higher response rate, but this was statistically significant in only one trial (60). The toxicity of doxorubicin-containing combinations was generally more pronounced, but the durations of response and survival seemed to be the same as with other drug combinations. CMF or CMF modifications seem to be more or less non-cross resistant to the doxorubicin-containing combinations. Oncologists therefore often give doxorubicin combinations as first line chemotherapy and CMF as second line or vice versa. There seems to be no compelling reason for one or the other choice. Based on the hypothesis advanced by GOLDIE & COLDMAN (30), alternation between the two non-cross resistant regimens has been evaluated, but not found to be more efficient than sequential treatment (1, 6, 8).

The schedule of administration could be of importance both with regard to efficacy and toxicity. In two trials comparing the original Cooper regimen, which involved almost continuous chemotherapy, with more intermittent regimens, the more continuous was superior (39, 61) both with regard to RR and toxicity, but with no difference in survival. Weekly administration of doxorubicin has been used for the past 10 years (23, 25, 26, 70, 71). A dose of 12 to 14 mg/m^2 has been given while the traditional dose of doxorubicin in most combinations is approximately 50 mg/m^2. In a prospective randomized study started in 1982, weekly doxorubicin was compared with the VAC regimen. A series of 128 patients were randomized to either weekly doxorubicin (n=62) or VAC (n=66). The RR's were 31 and 35 per cent, respectively, with no difference with regard to number of complete remissions, duration of response, or survival. Toxicity was considerably lower for weekly Adriamycin. With the possible exception of patients with extensive liver metastases, bone marrow depression was negligible. In contrast, most of the VAC patients experienced severe toxicity including nausea, vomiting and alopecia (33). Subgroups of patients, such as those with liver metastases, were also analyzed and no significant differences with regard to therapeutic efficacy were found between the two regimens.

However, frequent administration of doxorubicin might reduce patient compliance and also increase the risk of extravasation. Some of these problems can be solved by implantation of a vascular access port (10, 53, 62). A combination of 5-FU and mitomycin-C (FuMi) has been evaluated as second line chemotherapy in hormone resistant patients (44). The response rate to this treatment was approximately 20 per cent. It was well tolerated. Although thrombocytopenia was found in 5 to 10 per cent of the patients, this in no case gave clinical symptoms. The study also indicated that weekly doxorubicin and FuMi are non-cross resistant regimens.

Effective new drugs

During the past few years, much interest has been focused on mitoxantrone, an anthracenedion derivative, and the anthracyclin derivative 4-epidoxorubicin (17, 34, 73). It is too early to draw definite conclusions concerning the value of these drugs in advanced breast cancer. They both seem to compete with doxorubicin with regard to therapeutic effect and a more favourable toxicity profile has been claimed for both drugs. When mitoxantrone was compared with doxorubicin as single drug treatment (37), mitoxantrone gave a somewhat lower response rate (25 vs 35%) and shorter response duration (154 vs 231 days). However, these differences were not statistically significant and no survival difference was found. The toxicity rate, especially vomiting (7 vs 31%) and alopecia (5 vs 66%), was significantly lower in the mitoxantrone treated patients. In a randomized trial CAF was compared with the same combination, with Adriamycin replaced by mitoxantrone (CNF). There was no difference with regard to response rate, duration of response, or survival. The CNF combination was significantly less toxic than the CAF combination (14).

4-epidoxorubicin appears to have anti-tumor activity similar to the parent compound doxorubicin. When tested in a combination with 5-FU and cyclophosphamide (FEC) and compared in a randomized study vs FAC with equimolar doses (50 mg/m^2) of 4-epidoxorubicin and doxorubicin, response rates were comparable (49 vs 52%) with less nausea and vomiting, alopecia, and myelosuppression in the FEC combination. These data might suggest a better therapeutic index for FEC than for FAC (3).

Conclusion

Response rates for patients treated consecutively will vary around 35 to 40 per cent and last for 6 to 12 months. Single drug treatment with weekly fractionated doxorubicin seems to be comparable to combination regimens and is far less toxic. Response rates for second line chemotherapy are lower with shorter duration, and have limited value, although the combination of 5-FU and mitomycin-C in some cases can offer meaningful palliation with moderate toxicity.

There seems to be general agreement that chemotherapy in breast cancer is only palliative. In spite of numerous new drugs and combinations, impact on survival has been only marginal. Thus it seems important to develop new and more effective drugs. In order to avoid erroneously rejecting new drugs they should be evaluated in patients not heavily pretreated. Based on the heterogeneity of breast cancer cells, it is conceivable that major progress in chemotherapy in patients with advanced breast cancer, especially with regard to the most important end point, i.e. survival, will come from a combination of several drugs. However, with the present drugs, it does not seem likely that any combination or schedule will significantly improve survival. Therefore, before new, more active drugs have been found, emphasis should be laid on regimens with comparable response rates and a minimun of toxicity, such as the weekly fractionation of doxorubicin and perhaps a wider use of drugs with less toxicity, such as 4-epidoxorubicin and mitoxantrone.

Request for reprints: Dr Stein Gundersen, Department of Medical Oncology and Radiation Therapy, The Norwegian Radium Hospital, N-0310 Oslo, Norway.

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