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Perspectives and Commentaries

Clinical Trials in Advanced Breast Cancer

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(A COMMENT ON: Gundersen S., Kvinnsland S., Klepp O. *et al.* Weekly adriamycin versus VAC in advanced breast cancer. A randomized trial. *Eur J Cancer Clin Oncol* 1986, **22**, 1431–1434.)

In spite of all therapeutic efforts, metastatic breast cancer is still an incurable disease. For patients presenting with clinically advanced disease, failing on hormone therapy or having tumors that lack hormone receptors, chemotherapy is the only available treatment, leading to an effective but temporary palliation of symptoms in 40–60% of cases [1].

Heterogeneity of the disease makes treatment evaluation difficult, while several factors have been shown to influence response to cytotoxic drugs. Factors associated with a poor response to chemotherapy and a short duration of survival include a poor performance status, the presence of visceral metastases, prior failure to chemotherapy, extensive disease involvement and prior radiotherapy. Moreover, within the group of patients with visceral metastases one should distinguish several prognostic subgroups such as those with predominant liver involvement versus patients with pleural effusion. Age, menstrual status, extent of axillary node involvement and size of the primary tumor have no influence on the response to chemotherapy [2].

Considering the fact that the impact of chemotherapy on the overall survival of patients with advanced breast cancer varies between different subgroups, it is very important to evaluate the results of clinical trials according to specific prognostic categories of patients.

Apart from the analysis of survival figures, the number of complete responses is also relevant when the long-term impact of therapy is being considered. Usually, there are significant differences in median survival when responders and non-responders are compared, but these differences are more evident when patients entering into complete remission are compared to other subgroups [3]. As it has been clearly demonstrated in diseases such as acute lymphoblastic leukemia and Hodgkin's lymphoma, the increase in the number and in duration of the complete remissions is an essential step to reach curability in disseminated malignancies. Therefore, the low complete remission rates now achieved with chemotherapy in patients with advanced breast cancer may explain its modest impact on survival figures [4].

Another important aspect in the analysis of results in breast cancer is the definition of the duration of response. It may be quite possible that patients receiving treatment earlier in the course of the disease, more often achieve complete remission due to the presence of a lower tumor burden at the start of treatment. Thus, the duration of survival should preferably be counted from the time of initial metastases and not from the start of chemotherapy.

While there is no doubt that chemotherapy may prolong survival of some patients with advanced disease, particularly those with life-threatening rapidly developing visceral metastases, other prognostic factors may be more important than cytotoxic therapy for other categories of patients. The apparent paradox of increased median survival with no obvious impact on the overall survival can be explained by the benefit of treatment in responding subgroups being outweighed by the harm done to others, for whom survival may even be shortened.

Treatment related toxicity is extremely important to be analysed when aggressive therapy has to be given to patients with such an incurable disease

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as advanced breast cancer. Whenever the goal of therapy is only the symptomatic control and not an attempt to increase the duration of survival, there is usually no advantage to an aggressive chemotherapy regimen. Effective palliation is sometimes achieved with less toxic combinations or even with the use of single agent therapy [5].

In a previous issue, Gundersen *et al.* [6] reported on the similar effectiveness but markedly reduced acute toxicity of a weekly low-dose doxorubicin schedule, studied in a randomized trial against vincristine-doxorubicin-cyclophosphamide (VAC) given as 3-week courses in patients with advanced disease. This interesting study brings to our attention the question of what is the most effective chemotherapy in metastatic breast cancer, and also the successful approach to decrease doxorubicin toxicity by using a weekly low-dose schedule. Therefore, we wish to briefly comment on the status of chemotherapy in advanced breast cancer and on the strategies for further improvement.

The drugs that have been used most commonly in breast cancer include cyclophosphamide, methotrexate, 5-fluorouracil, doxorubicin and vincristine. Although with single agent treatment objective responses have been demonstrated in 15–45% of cases, these responses are usually partial and of short duration. Doxorubicin is probably the most active single agent in this disease, producing objective responses in 35–45% of patients, with 10–20% complete remissions and a median duration of responses of 5–8 months [7].

Combination chemotherapy has produced higher response rates than single agents but there is still no evidence that combinations increase the number of complete responses, when compared to doxorubicin alone [8]. Therefore, it seems appropriate for this agent to serve as a control arm in randomized trials studying doxorubicin-containing combinations in advanced breast cancer.

Currently, the most commonly used combination regimens in advanced disease are cyclophosphamide-methotrexate-5-fluorouracil (CMF) and cyclophosphamide-doxorubicin-5-fluorouracil (CAF) which produce objective responses in 40–70% and 50–80% of patients, respectively [1, 5].

Although the response rates and the number of complete remissions to CAF appear superior to CMF, there is no significant difference in the duration of response between the two regimens in randomized trials. Because of their higher initial response rates, doxorubicin-containing combinations should be applied in patients with extensive and rapidly progressive disease, weight loss, liver involvement and poor performance status, requiring an effective and rapid reversal of the fulminant course of the disease.

In order to analyse the results of the study reported by Gundersen *et al.* [6], one may argue that the number of patients in each treatment arm of this randomized study in this heterogeneous disease should have been larger, to make the conclusion more meaningful. Also, the characteristics of the patients included in the trial should have been discussed in more detail, in particular the specific sites of involvement within the group with visceral metastases. Although, there were no marked differences between the two arms with regard to various prognostic factors, it would have been helpful if the effects of treatment in each specific risk-group had been presented.

The presence of visceral involvement in 50% of patients in both arms and the long interval from relapse until the start of chemotherapy may explain the relatively low response rates and the limited number of complete remissions observed by the authors. Weekly doses of doxorubicin between 6–12 mg/m^2 have been described to produce objective responses in more than 50% of patients, with a median duration of remission of 12 months and these results have been confirmed in a randomized trial comparing weekly low-dose doxorubicin versus CAF [9, 10]. In the latter trial, responses were shown even in patients who had received prior doxorubicin in conventional doses. Furthermore, in another study objective responses were reported in 27% of patients previously treated with chemotherapy [10]. In the present trial, less than 20% of cases had received prior cytotoxic agents but none had been exposed to doxorubicin.

Although VAC has been reported to produce objective responses in the same range as other doxorubicin-containing programs, the inclusion of vincristine does not appear to add an advantage to the other two agents in randomized trials [11]. When responses to vincristine alone are demonstrated, they are mostly dependent on a weekly schedule, which is usually followed by severe neurotoxicity.

As stated by Gundersen *et al.* [6], the relatively low response rates observed in their study could have been related to the long interval from the first metastases until the start of treatment, which could suggest the presence of a higher tumor burden, compared to patients receiving earlier treatment. As discussed above, the best way to overcome such methodological problems would be the separate evaluation of responses by prognostic subgroups, and the evaluation of the duration of survival from the time of initial metastases and not from the start of the treatment.

The significant reduction in acute toxicity related to chemotherapy in the weekly low-dose schedule arm versus VAC confirms the results of previous studies [10]. The minimal gastrointestinal

and bone marrow toxicity and much less alopecia obviously favours the weekly low-dose schedule. Other studies have also shown a significant reduction in the incidence of doxorubicin cardiotoxicity with the weekly low-dose schedule [12]. Although this is extremely important for the quality of life of patients, it will not lead to a significant increase in complete remission rates or to cures. Probably, the search for new agents is more critical for further developments in the treatment of advanced breast cancer. Efforts must be concentrated on drug screening methods and on the evaluation of new compounds.

In conclusion, some interesting aspects of the current status on the treatment of breast cancer were highlighted by the above study. First, it supports previous reports showing a better therapeutic index of a weekly low-dose doxorubicin compared to the conventional doxorubicin schedule. As a result, a poorly tolerated active drug is turned into a more tolerable and safer treatment, without compromising antitumor activity. It also reminds us that studies in this heterogeneous disease should include a large number of patients per treatment arm, in order to create the possibility of performing a multivariate analysis. Furthermore, a detailed description of patient characteristics and prognostic factors, including response by site and the total dose administered, are essential for a proper evaluation of treatment results.

Finally, it is of great importance that larger studies with appropriate stratifications according to prognostic factors are initiated to confirm the findings of these authors prior to imply their conclusions as guidelines to treatment of the general patient with advanced breast cancer.

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