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Editorial

Multicenter vs single center phase II evaluation of 4′-iodo-4′-deoxydoxorubicin in advanced breast cancer

Phase II studies with antineoplastic agents are designed to provide an estimate of the level of objective activity of a candidate compound in a particular tumor type. These studies represent a key step in the decision-making process, since only compounds exhibiting significant antitumor activity at this stage will be considered for further development. Therefore, the design of phase II trials should be focused on methods that minimize the risk of overlooking active compounds while retaining the power to identify inactive ones at an early stage [1].

In order to reduce the risk of false negative compounds, phase II studies should include patients who are likely to be responsive to cytotoxic agents, such as those with a good performance status, a limited number of metastatic sites and minimal or no prior exposure to chemotherapy. In several studies of metastatic breast cancer, the above favorable characteristics were shown to increase the likelihood of tumor response [2].

In contrast, patients with breast cancer presenting with skeletal or hepatic metastasis, extensive prior exposure to cytotoxic drugs and/or radiotherapy, and a low peripheral lymphocyte count at the start of treatment were shown to have a reduced chance of tumor response to chemotherapy [3, 4]. Other factors such as age, menopausal status, disease-free interval or hormone receptor content in the tumor were not yet clearly established as having predictive value for sensitivity to cytotoxic agents [5].

Regardless of the degree of homogeneity of the sample population included in the trial, dose intensity of the treatment seems to be a major factor in achievement of a tumor response. In experimental tumor models, dose reductions of various cytotoxic agents such as cyclophosphamide, thiotepa or cisplatin were associated with a significant decrease in disease-free survival and curability [6]. Although animal studies cannot be directly translated into the clinical situation, analyses of data compiled from chemotherapy trials in patients with similar pre-treatment characteristics have suggested a strong correlation between dose intensity and response rates, disease-free survival and overall survival [7].

Dose-response relationships for anthracyclines can be illustrated by the results of a prospective trial performed in patients with metastatic breast cancer comparing doxorubicin given intravenously at two different doses, 35 mg/m^2 versus 70 mg/m^2, on a three-weekly schedule [8]. Fifty-eight percent of patients receiving the higher dose of doxorubicin showed objective responses against only 25% in the lower dose arm ($p < 0.02$). The median duration of responses was 14 months in the higher dose arm versus 6.5 months in the lower dose arm ($p < 0.01$). In addition, the median probability of survival was 20 months versus 8 months in the higher and lower dose arms, respectively ($p < 0.005$). Because of the obvious superiority of the higher-dose doxorubicin regimen, the trial was closed for ethical reasons after the accrual of 48 patients.

Two phase II studies of 4′-iodo-4′-deoxydoxorubicin (I-Dox) conducted in patients with advanced breast cancer are reported in this issue of the Annals of Oncology. Following an elegant phase I and pharmacokinetic study of I-Dox performed by investigators at the National Cancer Institute of Milan [9], Gianni et al. designed a phase II trial in which the drug was administered to a selected patient population at the maximum tolerable dose (MTD) of 80 mg/m^2 every three weeks [10]. The rationale for choosing the MTD of I-Dox for phase II evaluation was mainly the excellent tolerability of the drug during the phase I trial, especially the lack of significant non-hematological toxicity.

Concomitantly, Sessa et al. of the EORTC Early Clinical Trials Group conducted a series of multicentric phase II trials of I-Dox in patients with various tumor types, including breast cancer, in which the drug was given by the same schedule, but at the dose of 70 mg/m^2 [11]. Being a multicentric study, a somewhat lower dose of I-Dox, defined on the basis of another phase I trial performed by Alakl et al. in a less favorable patient population, was used [12].

Interestingly, a three-fold difference in objective response rates to I-Dox between the two trials, i.e., 35% in the Milan trial versus 10% in the EORTC trial, was reported. The above discrepancy in terms of response rates to the same agent in patients with advanced breast cancer provides an excellent opportunity to discuss the influence of patient selection and dose intensity upon tumor response to chemotherapy in multicenter versus single-center phase II trials.

Considering the limited number of patients included in phase II trials, the outcome of multicenter studies depends heavily on the results from each of the individual participating centers. Institutions entering only a minimal number of patients tend to have less experience in the handling of the compound under investigation, and a higher probability of treatment delays and protocol violations [13]. In EORTC multicenter trials, a significantly higher percentage of patients meeting the protocol requirements was found in participating institutions entering a larger number of patients, as opposed to those with low patient accrual [14]. Although

the details on patient accrual per institution were not reported in the phase II trial of I-Dox performed by the EORTC, the above factors should be considered in the interpretation of the results of both trials.

Performance status at the start of treatment was shown to predict for both response to chemotherapy and survival in patients with various types of malignancies, including breast cancer [3, 5]. In the I-Dox studies, patients in the Milan trial were scored according to the Karnofsky scale, while the WHO criteria was applied by the EORTC. In both trials, patients were described as having excellent performance status. However, dissection of the characteristics of patients in each trial suggests that patients included in the Milan study might have had a slightly better performance status, as judged by the younger median age, less aggressive visceral disease and only limited exposure to prior anticancer therapy. Thus, patients in the EORTC trial might have been somewhat less prone to respond to I-Dox than those in the Milan group because of a slight disadvantage in performance status.

Dominant site of disease and number of sites of metastatic involvement have also been shown to influence response rates and overall survival in patients with breast cancer. Women presenting with one or two metastatic sites at diagnosis exhibit a significant advantage in survival compared to those with three or more sites of involvement [15]. Notably, in the Milan trial, the breast (T4) was the main site of disease in 22/31 patients (55%), but in only 1/22 patients (4.5%) in the EORTC trial. In the latter study, 12/22 patients (55%) showed visceral disease at the time of accrual. Thus, patients in the Milan trial comprised a better prognostic group for response to chemotherapy than the EORTC patients, as reflected by a favorable distribution of dominant sites of disease.

The question of whether prior adjuvant therapy may influence the rate of response to chemotherapy in patients with breast cancer is still debatable [16, 17]. Prior exposure to anthracyclines was an exclusion criterium in the I-Dox studies, and only 24% of the patients in the Milan trial received adjuvant CMF chemotherapy. In this trial, I-Dox was the first anticancer drug to be administered to 67% of the patients. Also, radiotherapy was administered in only 18% of patients. In contrast, 41% of the patients had received prior adjuvant CMF chemotherapy in the EORTC trial, while 50% of them had previously been exposed to one or more palliative endocrine treatments. Thus, the patient population of the Milan study had had less prior exposure to cytotoxic therapy than those in the EORTC trial.

However, other factors such as the higher dose intensity applied in the Milan trial might have played an even more important role. In that study, patients received I-Dox at the MTD of 80 mg/m^2 at three-weekly intervals, with grades 3 and 4 granulocytopenia occurring in 41% and 34% of the cases, respectively. In contrast, in the EORTC trial, a lower dose intensity of drug delivery was achieved, as judged by the selection of a lower administered dose, the higher number of courses in which doses were reduced, and the lower percentage of episodes of grades 3 and 4 granulocytopenia, i.e., 32% and 14% of courses, respectively. Therefore, the discrepancies in objective response rates, if real, could be attributed to factors such as patient selection and differences in dose intensity between the two treatments.

In addition to the above factors, methodological aspects related to the design of phase II trials should be taken into consideration in the interpretation of response rates to chemotherapy. Hypothetically, if the 10% objective response to I-Dox reported in the EORTC trial were the only factor in the decision regarding its further clinical development, the compound would certainly be dropped. However, the 35% of objective responses of the Milan trial would suggest otherwise, especially considering the more favorable non-hematological toxicity profile of I-Dox as compared to doxorubicin. Interestingly, even here premature assessment of the results could be misleading. The 95% confidence interval calculated for responses in both trials, i.e., 10% and 35%, are large enough to cover a range of responses from 20%–30% (1.2%–32% and 21%–53% in the EORTC and Milan trials, respectively). Thus, the differences in response rates between the studies could be independent of patient selection or dose intensity, reflecting only statistical variability.

I-Dox, an analogue of doxorubicin, was selected for clinical evaluation on the basis of the superiority of its therapeutic index to that of the parent drug, as well as its sensitivity to doxorubicin-resistant experimental tumors [18]. From a methodological perspective, phase II trials of analogues such as I-Dox should preferably have a prospective randomized design, with doxorubicin as the control arm. Since patient characteristics are expected to be randomly distributed, this approach may reduce the risk of false negative results due to differences in prognostic factors between the groups [19].

For logistical reasons, the above method is applied only infrequently in the design of early phase II trials. In fact, the extent of the initial evaluation of new agents needs to be balanced against the large number of compounds entering clinical testing and the limited patient and financial resources. In view of the fact that significant antitumor activity is documented in only a small percentage of patients in early clinical trials, phase II studies are usually designed in such a way as to provide an estimate of the level of tumor responses, including the minimum number of patients needed to avoid unnecessary exposure to inactive compounds. If worthwhile antitumor activity is observed for a new compound at an early stage, a more detailed clinical evaluation is then pursued.

A disease-oriented non-randomized design focused on the tumor types most frequently encountered in the clinic is currently being adopted for early phase II trials by the EORTC and most research institutions [20]. A

Gehan's two-stage design is usually applied in such a design [21]. For example, if the minimum percentage of response considered of interest for a new compound is 20%, then 14 consecutive patients are accrued in the first stage. If no response is documented, the compound is labeled as inactive and the trial is terminated. Here, the statistical assumption is that agents producing at least a 20% response rate are expected to have a 95% chance of showing activity in at least one out of 14 consecutive patients. Hence, if a new compound produces no response in the first 14 consecutive patients, it can be dropped from further development with a chance of yielding a false negative not greater than 5%.

Compounds producing at least one objective tumor response out of 14 patients are then brought into the second stage of Gehan's design, where additional patients are included in the trial, to allow a better estimate of the level of responses to the new compound. Not infrequently the above statistical method is erroneously applied, for instance, by accrual of a highly heterogeneous set of patients in the first stage. In such case, there is a chance of observing no response in the first 14 patients with an active agent (false negative result). This situation is certainly more frequent in multi-center than single-center trials, because of the differences in patient selection among the participating institutions.

Similarly, by relying exclusively upon the results obtained in the first stage, inactive compounds could be accepted as marginally active, in view of the fact that a compound showing even a 5% objective response rate has about a 50% chance of producing at least one response in 14 patients (false positive result). Therefore, completion of the second step, with the inclusion of additional patients up to the optimal number necessary to estimate the level of responses to the new compound, is critical for the quality of the trial [22].

In the case of a doxorubicin analogue such as I-Dox, the minimum level of responses considered to be of clinical interest in patients with advanced breast cancer is about 30%. That level is based on the minimum objective response rates obtained with doxorubicin in routine oncology practice, which is to say that compounds with an inferior level of activity are not considered as a priority for further clinical development. Obviously, the spectrum of activity, and pattern of toxicity of the new agent are also taken into consideration in the decision regarding its further evaluation [23].

Past experience clearly illustrates the importance of using extreme caution in the decision-making process of phase II trials. Initial studies with cisplatin showed very modest activity against tumors included in its preliminary evaluation, and the toxicity profile of this agent was regarded by many experienced investigators as a reason to discontinue its clinical development. Fortunately, the testing of cisplatin in patients with germ-cell tumors yielded impressive results and additional trials in other tumor types, such as ovarian cancer, bladder cancer and head and neck cancer, aided by the use of pre-hydration procedures to minimize the risk of nephrotoxicity, have allowed confirmation of the high level of activity of this agent in a variety of tumor types [24].

In conclusion, the estimation of objective responses to new agents in early phase II trials should be interpreted with great caution. Common sense would suggest that the prospects of new candidate compounds should be judged not only on the basis of results of isolated trials, but on a balanced review of the available data from several studies performed at different institutions. The poor response rate of I-Dox in patients with advanced breast cancer in the EORTC trial discussed in this issue of Annals of Oncology is probably related to problems of patient selection and dose intensity which tend to occur more often in multicenter phase II studies. The level of antitumor activity and lack of significant non-hematological toxicity of I-Dox observed in the Milan trial makes it a potential candidate for dose intensity studies in combination with hematopoetic growth factors. These trials will be activated at the National Cancer Institute in Milan in the near future.

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