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Perspectives and Commentaries

Evaluation of New Agents in Breast Carcinoma and Other Chemotherapy-sensitive Tumors

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INTRODUCTION

MEDICAL therapy of breast carcinoma has progressed substantially since the first demonstration of the activity of the alkylating agents in the late 1950s and early 1960s. Freckman *et al.* in one of the early studies, reported an 'objective regression' rate of 34% with chlorambucil and prednisolone [1]. Subsequently, a wide variety of antitumor agents were found to have activity against this disease, including 5-fluorouracil, methotrexate, vincristine and adriamycin [2]. The application of the principles of combination chemotherapy as first devised for the treatment of hematological malignancies represented a major advance. Cooper first reported a response rate of 88% with the combination of cyclophosphamide, methotrexate, 5-fluorouracil, vincristine and prednisone [3]. Numerous investigators pursued this initial promising lead with a variety of modified 'Cooper regimens'. In most series, response rates of 50-70% have been achieved and the median survival of all patients has varied from 12 to 21 months. It is true that response rates lower than 50% have been observed by some investigators, usually because their dosage schedules were substantially lower than those proposed originally by Cooper.

The introduction of adriamycin marked the advent of a new era in breast cancer chemotherapy. This drug is the most active single agent for the treatment of this malignancy [4]. Soon new regimens were proposed which incorporated adriamycin, usually in combination with 5-fluorouracil and cyclophosphamide [5]. Most investigators have reported response rates of 60-84% and the median survival of all patients has generally varied from 14 to 27 months. Again, a few investigators have reported lower response rates when less intensive dosage regimens have been administered.

Despite these favorable results, much remains to be accomplished. The high response rates consist primarily of partial remissions and only about 20-25% of patients achieve complete remissions with currently available chemotherapeutic regimens. Legha *et al.* reviewed the experience at our institution in 116 patients with metastatic breast carcinoma who achieved complete remissions with various 'FAC' regimens [6]. Less than 40% of these patients remained in complete remission after 2 yr and about 20% after 3 yr. The hazard of relapse remained relatively constant after the first 6 months of remission, suggesting that few, if any, patients were actually cured of their disease. In another study Decker *et al.* reported a complete remission rate of 11% in 438 patients, with only 1 patient remaining free of disease at 6 yr [7].

The discovery of new agents with activity against breast carcinoma remains a research activity with the highest priority. The first phase of investigation of a new drug (the 'phase I trial') is conducted in patients with advanced malignancies for whom no effective therapy exists. Although it is hoped that some patients may benefit by participating in such trials, the likelihood of discovering substantial antitumor activity at this phase of clinical investigation is small. What is accomplished in the phase I trial is the determination of an approximate appropriate dose for subsequent investigations and the dose-limiting toxicities.

The next step in the evaluation of a new drug is the phase II trial, at which point a concerted effort

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is made to determine the degree of activity of the drug against specific tumors. The methodology of conducting such studies has become a matter of controversy. Historically, phase II trials were not separated from, but actually a continuation of, phase I trials. Once the appropriate dosage schedule was determined, large numbers of patients with a variety of refractory tumors were treated. However, there was a major problem with this study design. Although large numbers of patients were treated, often inadequate numbers of patients with specific malignancies were included to provide a correct assessment of the drug's activity even against some of the common malignant diseases. In order to avoid this problem, the phase II trial was separated from the phase I trial. A number of 'signal tumors' were selected (including breast carcinoma) and it became customary to prepare separate protocols for each disease. This approach ensured that adequate numbers of patients with each of the signal tumors would be studied and the drug's activity could be determined against all of them.

A major controversy has erupted over the issue of what type of patients constitute an appropriate group for entry on a phase II trial. One of the earliest controlled trials was a prospective randomized comparative trial of methotrexate and 6-mercaptopurine in acute leukemia [8]. Patients failing to respond to the initial drug were subsequently given the second drug. In that study the response rates for each drug were similar, whether they were administered as initial or subsequent therapy. The investigators concluded that this was a reasonable expectation when study drugs have different mechanisms of action and that 'the testing of new agents late in the course of acute leukemia is meaningful'.

As multiple drugs have become available for chemotherapy-responsive tumors, the problem has become more complicated. The usual patient has experienced multiple relapses before becoming available for entry on a phase II trial. Indeed, with current combination regimens for induction and maintenance therapy, it is not uncommon for a patient to have been exposed to six or eight different drugs by the second relapse. There is legitimate concern that such patients might be unlikely to respond to any subsequent therapy, no matter how effective. Consequently, using such 'far-advanced' patients might prevent recognition of an effective new agent. Certainly, this is likely to be the case if the new agent has a mechanism of action which is similar to that of an agent the patient has previously received and to which his tumor is no longer responsive. However, cross-resistance may exist due to other factors such as cell membrane permeability even when agents have different mechanisms of action. *In vitro* studies have shown cross-resistance between adriamycin and vincristine, agents which have completely different mechanisms of action [9]. Additionally, patients who have received multiple prior therapies usually have extensive disease, functional impairment of multiple body organs and compromised bone marrow reserves, making it difficult to administer these new agents at optimum dosage schedules.

Some clinical trials have shown that response rates with new agents are substantially higher in patients who have received minimal or no prior therapy when compared to patients who have received extensive prior therapy. For example, Gralla *et al.* evaluated vindesine in lung cancer and reported a response rate of 33% among previously untreated patients vs 12% among previously treated patients [10]. Similarly, the response of patients with breast cancer to bisantrene was lower among patients who were refractory to doxorubicin (9 vs 50%) [11]. For chemotherapy-responsive tumors additional chemotherapy-related factors have been identified as important prognostic variables. For example, in patients with malignant lymphoma Cabanillas *et al.* found that response to subsequent therapy was related to the quality of response to initial chemotherapy, duration of response to previous therapy and number of prior therapies [12].

Increasingly, the scientific objectives of clinical investigation and the ethical responsibilities of the physician to his individual patient are being drawn into conflict. In the case of breast cancer, combination chemotherapy is clearly superior to single-agent chemotherapy, with respect to both response rates and duration of response. For example, Smalley *et al.* compared five-drug chemotherapy to 5-fluorouracil [13]. The response rate with the optimum combination was 46% compared to 18% with the single agent. The median duration of response was 28 vs 16 weeks respectively. Mouridson *et al.* randomly assigned patients to receive a five-drug combination or cyclphosphamide alone [14]. The combination regimen was significantly superior with respect to response rate (63 vs 25%) and duration of response (median, 400 vs 210 days). Hence any study design which prevents the patient from receiving combination chemotherapy initially jeopardizes the patient's probability of responding, which ultimately may affect her survival. Secondly, is it justified to subject a patient to a new agent with an unknown response rate and poorly defined toxicity (especially cumulative toxicity) when agents with defined activity and toxicity are available?

It could be argued that patients with slow-

growing tumors would be appropriate candidates for new agents as initial therapy because they are not likely to die of their disease if they fail to respond to their initial treatment. Although the risk of early death from tumor progression may not exist in these patients, there are other risks. The patient could die from an unknown toxicity of the new drug or exposure to the new drug might interfere with the success of subsequent therapy without benefiting the patient. For example, a prospective randomized trial comparing the new anthracycline analog, carminomycin, with adriamycin was conducted in previously untreated patients with soft tissue sarcomas [15]. The response rates were 3 and 29% respectively. Only 6% of those patients who failed to respond to carminomycin subsequently responded to adriamycin. Hence only about 10% of patients treated initially with carminomycin ever achieved a chemotherapy-induced response. Combination chemotherapy with adriamycin, cyclophosphamide, vincristine and dacarbazine administered at optimum dosage has produced responses in about 45% of patients [16].

Of course, there is always the possibility that the new phase II agent could be more effective or less toxic than currently available agents, in which case the use of the new drug might be advantageous. However, even this potential advantage is offset by the fact that if the agent is used alone, such an eventuality would be extremely unlikely. Furthermore, past experience indicates that less than 20% of new drugs prove to have any useful activity, and obviously all drugs are not equally effective against all malignancies.

Another justification that has been proposed is that each individual owes a debt to society, and therefore, even if he does not benefit from a treatment himself, society as a whole will benefit from the knowledge derived thereby. This principle has been applied in many non-medical areas of society. For example, during war, young men are required to serve in the army and may die in the defense of their country. However, the physician's *primary* responsibility is to his individual patient and not to society. The doctor-patient relationship is based upon the patient's trust that the doctor will act in his best interests. The commonly accepted ethical standards of Western civilization are primarily derived from the Jewish and Christian Scriptures which emphasize the worth of the individual.

What is the solution to this problem? First, physician investigators must affirm the principle that no protocol and no scientific investigation should interfere with the individual patient's best medical care. Based upon past experience and known prognostic factors, it is possible to identify those patient populations who have a low probability of responding to existing therapeutic regimens. Where the probability of responding to new therapy approaches the probability of responding to currently available therapy, there is justification for evaluating the new therapy. In some diseases, such as colon carcinoma, response rates are low and responses are of short duration, hence new agents as initial therapy may be justified. In adult acute leukemia there are subpopulations whose response rates are so low that there is justification for giving new agents as initial treatment.

While conducting phase II trials only in previously treated patients with chemotherapy-responsive tumors may be scientifically undesirable, the patient's best interests require it. It can be acknowledged from the outset that such studies will underestimate the optimum response rate. It is unlikely that drugs with substantial activity will remain undiscovered because of this limitation. In these responsive tumors the primary objective is to discover new agents with *substantial* activity. Since multiple active drugs already exist, marginally active new drugs would be of little benefit unless they had other desirable features such as minimal toxicity. However, it is not necessary to exclude patients with chemotherapy-responsive tumors from phase II trials until they have received every conventional agent. Rather, they can legitimately be entered on phase II trials when the likelihood of responding to a new agent approaches the likelihood of responding to a conventional agent. Since combination chemotherapy is clearly more effective in responsive tumors, it is difficult to design trials to evaluate new drugs as initial therapy and provide the patient with optimum therapy. Probably the best compromise is to conduct a randomized trial in which the new drug is substituted for a conventional drug in a combination regimen.

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