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Optimising Treatment Outcomes: a Review of Current Management Strategies in First-line Chemotherapy of Metastatic Breast Cancer

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Metastatic breast cancer remains an essentially incurable disease and chemotherapy, despite producing frequent and clinically useful responses, has had a disappointing impact on survival. Several highly promising lines of clinical research with new agents, combinations and dosages may yet produce an improved outcome. Of the new drugs that have been studied, the taxoids, docetaxel and paclitaxel appear to be the most active agents yet discovered in this setting; navelbine is also active. Investigations of high-dose chemotherapy have produced the highest rates of complete response achieved in patients with this condition. The results of recent randomised trials confirm the high activity of this modality and also suggest a survival advantage compared with more traditionally dosed treatment. Active research into biological therapy is also under way and vaccines, antibodies and inhibitors of growth factors are all being evaluated. © 1997 Elsevier Science Ltd.

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INTRODUCTION

DESPITE THE availability of numerous active hormonal and cytotoxic therapies, treating metastatic breast cancer remains one of the most frustrating challenges in contemporary oncology. Endocrine therapies produce responses in approximately 30% of unselected cases and in 50–60% of those whose tumours express steroid hormone receptors. However, using modern response criteria, it seems possible that these estimates of response rates to hormone therapy may be revised downwards. The median duration of response to endocrine therapy is approximately 10–12 months and some patients will have secondary responses to salvage endocrine therapies at relapse [1]. For patients who fail while receiving endocrine therapy, for those with receptor-negative tumours, and for patients in whom impending visceral crisis mandates a rapid response, chemotherapy is generally indicated.

With modern combination regimens, the majority of patients can now be expected to achieve objective tumour regressions; complete regressions are achieved in approximately 10–15% of cases. These responses can have substantial palliative benefit in that they can ameliorate the distressing symptoms of widespread cancer, especially pain and dyspnoea [2]. These combinations may also delay impending organ failure and there is evidence that they might also prolong survival [3]. Oncologists commonly find that some patients, for whom death appears to be imminent, can be 'salvaged' with chemotherapy and restored to reasonable health for periods of time that can, on occasion, be of several years' duration. Indeed, a very small minority of patients with stage IV disease appear to achieve such prolonged remissions that it is tempting to speculate that the condition is, in exceptional circumstances, curable. Unfortunately, the overwhelming majority of complete and partial remissions end in relapse, and the median duration of survival from the time of diagnosis of metastatic disease is in the range of 1–3 years [4].

The mechanisms by which cancer cells survive the lethal effects of cytotoxics are collectively referred to as drug resistance. Classic combination chemotherapy theory and practice is based on the assumption that the co-administration of a number of different agents that are putatively susceptible to different resistance mechanisms would increase the likelihood that a tumour would be eradicated [5]. Thus, the introduction of new agents into existing active anti-breast cancer regimens might in theory result in cure. In fact, one of the more depressing aspects of the history of chemotherapy for stage IV disease has been the modest survival impact of new drugs in this setting. Doxorubicin is a case in point. This drug, which was introduced into widespread investigative and clinical practice in the 1970s, was clearly the most active single agent then available for the treatment of this disease; response rates of 50–60% were reported. More impressive was the observation that patients whose disease had relapsed following, or was refractory to the then standard alkylating agent/antimetabolite regimens (e.g. cyclophosphamide-methotrexate-5-fluorouracil, CMF), could achieve responses—

sometimes complete—with doxorubicin [6]. In view of the experience of treatment with multi-drug regimens in lymphomas and leukaemias, it was hoped that similar programmes in which doxorubicin was co-administered with these older active drugs might increase the rate of durable remissions and speculatively might make metastatic breast cancer a curable condition. While higher response rates were in fact reported, the survival impact of doxorubicin-containing combinations was strictly limited [7]. Thus, it appeared that while the disease was superficially responsive to existing treatments, it might somehow be fundamentally incurable in the majority of cases.

While this nihilistic interpretation achieved a widespread currency, clinical research continued to progress along several diverse lines. There was still a possibility that the classic developmental chemotherapy approach might produce cytotoxics of such high activity that substantial advances might yet occur. Other areas of active research include biological therapies and attempts to exploit the increasingly recognised relationship between chemotherapy dose and schedule and the anti-tumour effect.

NEW DRUGS

Several new drugs have demonstrated substantial activity in metastatic breast cancer. The taxoids, docetaxel and paclitaxel, have emerged as particularly useful agents in the treatment of this disease. Early studies with paclitaxel in previously untreated patients used a 24-hour infusion schedule, and objective response rates of 50–60% were reported [8]. Shorter infusions appeared to be less active [9]. Docetaxel, which can be administered over 1 hour, produced response rates of 50–60% [10, 11]. Responses were seen in all metastatic sites, including the liver. Particularly impressive was the fact that these drugs had substantial activity in patients whose disease had relapsed following, or was resistant to, prior anthracycline-based therapy [12]. While these drugs are now generally regarded as being the most active chemotherapeutic agents that are currently available for the treatment of metastatic breast cancer, it must be stated that the duration of responses they produced were not obviously superior to those reported for older treatments and durable remissions remained rare.

Combinations of taxoids with other active agents have been studied. Regimens that included anthracyclines have been the subject of particular interest because of the above-mentioned incomplete cross-resistance that has been demonstrated between these drugs. In a phase I study carried out at the United States National Cancer Institute, patients received simultaneous 72-hour infusions of doxorubicin and paclitaxel. Diarrhoea and typhlitis were dose-limiting and, disappointingly, the activity of the combination did not appear to be higher than that of established doxorubicin-containing regimens [13]. Gianni and colleagues in Milan, Italy, studied short infusion (3-hour) paclitaxel with doxorubicin. In this study, a relatively high incidence of cardiac toxicity was encountered, but the regimen appeared to be exceptionally active. The overall response rate was 94% and, impressively, the complete remission rate was over 40% [14]. Preliminary data from studies of paclitaxel with epirubicin suggest that this regimen is also very active and may have a more favourable therapeutic ratio [15]. The combination of docetaxel with doxorubicin may also be highly active [16]. Cisplatin is another agent with prominent activity in breast cancer, although its formidable toxicity profile and the availability of other active agents has limited its use in this disease [17]. The combination of cisplatin and paclitaxel has been reported to produce responses in 48% of patients with metastatic disease [18]. Haematopoietic growth factors have been shown to facilitate the administration of high doses of cyclophosphamide with paclitaxel, and this combination may also be worthy of study in metastatic breast cancer [19].

Another agent that has been demonstrated to have substantial activity in metastatic breast cancer is vinorelbine (Navelbine®). The response rate to vinorelbine, when given as a single agent, is approximately 40–50% and combinations of navelbine with other drugs are being actively explored [20].

While it is still possible that one or other of these combinations might substantially improve the outcome of patients with metastatic breast cancer, it seems more likely that their greatest impact will be in adjuvant treatment of earlier stage disease, in which studies are currently under way.

CHEMOTHERAPY DOSE AND SCHEDULE

The existence of a relationship between drug dose and efficacy is a fundamental principle in human pharmacology. Chemotherapy dose has been demonstrated to be an important determinant of anti-cancer effect in preclinical systems, although the degree of dose-escalation required to produce meaningful differences in cell kill is relatively large [21]. In the clinic, prospective random assignment studies that explored doses within the 'conventional-dose' range in patients with metastases produced modest and somewhat inconsistent results [22–25]. The degree of dose-escalation that was achieved in these trials was, however, far lower than that which had been studied in the laboratory.

The development of marrow autografting facilitated the study of very high doses of some drugs, principally the alkylating agents and allowed clinical investigators to mimic the levels of drug exposure that had been achieved in the laboratory. The first trials of high-dose chemotherapy in breast cancer were performed in patients with disease who had failed to respond to conventional treatment [26]. While high rates of response were achieved, confirming that dose-escalation could indeed partially overcome drug resistance, they were of brief duration and were associated with treatment-related mortality in up to 20% of patients. In subsequent studies in the setting of newly diagnosed metastases, remissions were seen in approximately 50% of patients and, provocatively, a minority remained durable [27, 28].

In an attempt to improve on these results, investigators turned to applications of mathematical models of tumour growth kinetics. Throughout the 1960s and 1970s, the most widely accepted explanation of tumour growth was the exponential model of Skipper and Schabel [29]. According to this model, tumours had a constant growth rate and, in turn, regressed according to first-order kinetics, i.e. a constant proportion of cells were killed by a treatment, regardless of the size of the tumour. This model provided a compelling rationale for the concept of post-surgical 'adjuvant' chemotherapy for earlier stage breast cancer in that it was believed that a treatment that could produce a clinical response in patients with overt metastases might be curative in a patient with clinically undetectable micro-metastases. However, the clinical impact of adjuvant chemotherapy, while important, was less than might have been expected, indicating that the

exponential model might not represent the full reality of tumour kinetics [30].

In considering this paradox, it was proposed that cancer cells grew and regressed, not in a strictly exponential fashion, but in a Gompertzian manner, i.e. one in which the growth rate decreases with increasing tumour size. Furthermore, they expanded on the dose–response concept by hypothesising that the rate of regression of a cancer was related both to the dose of chemotherapy administered and to the growth rate of the unperturbed tumour at that phase of its growth curve. According to this model, small, fast-growing tumours should be more sensitive than large, slow-growing ones comprising otherwise identical cells. Sub-clinical tumours can have such a high growth rate, however, that their eradication becomes, paradoxically, more difficult to achieve mandating a phase of 'late intensification' [31].

In the 1970s and 1980s many groups studied this approach in patients with various cancers. In trials in patients with both metastatic [32] and earlier stage cancer, doxorubicin-based therapy was used as the late-intensification [33]. While these trials were positive the benefit was relatively modest, indicating that the level of late-intensification that had been achieved was insufficiently high to have a meaningful impact on drug-resistance. Thus, there was a compelling rationale for using high-dose chemotherapy with autograft support as a form of late-intensification in patients who had responded to standard-dose induction chemotherapy.

This strategy, which would also facilitate the identification of those patients with resistant disease who had previously been shown to have poor outcomes with high-dose chemotherapy, soon became the dominant model and it produced relatively consistent results. Complete response rates were approximately 50–70%. Disappointingly, most of these remissions still ended in relapse and as treatment-related mortality declined with the introduction of peripheral blood progenitors [34–36], such relapse emerged as the leading cause of treatment failure.

Overall, the results of induction/late-intensification were not convincingly superior to those reported for high-dose chemotherapy without prior induction. Nevertheless, the occurrence of durable remissions in 10–20% of patients suggested the possibility that this might be a curative treatment for some patients with metastatic breast cancer [37–39]. There was general acceptance of the need for prospective randomised trials to verify the results of these possibly biased historically controlled studies [40]. However, even if such verification was obtained, high-dose chemotherapy would remain a relatively poor treatment for metastatic breast cancer because of the low percentage of durable remissions.

An interpretation of these results, based on the Goldie-Coldman model, would suggest that relapse following high-dose chemotherapy was inevitably due to the persistence or emergence of clones of cancer cells that were absolutely resistant to the drugs used in the high-dose therapy [41]. In an attempt to overcome this problem, Gianni and colleagues devised innovative regimens that sequentially delivered high doses of different single agents that were putatively susceptible to different drug-resistance mechanisms. These programmes have produced encouraging results in node-positive breast cancer [42] and have been adapted for study in metastatic disease [43]. This 'high-dose sequential' model, like the induction/consolidation strategy, is, however, based on the premiss that populations of cells that are sensitive to a treatment can be efficiently eradicated by a single application of that treatment, a proposition that has not been well demonstrated in other cancers [44]. The cure of Hodgkin's disease [45] and testicular cancer [46] resulted from the identification of highly active regimens and the application of a sufficient number of cycles of those regimens to eradicate the cancer. As the high-dose programmes appear to be the most active regimens currently available for the treatment of metastatic breast cancer, would it not be logical to treat patients with multiple cycles of these highly active regimens rather than prefacing their use with treatments which, in the context of cure, are highly ineffective?

This approach might in fact be more consistent with the Norton–Simon model, the ultimate logic of which is that all treatment courses should be given in high dose. Furthermore, the observation that Gompertzian kinetics predicted rapid regrowth of small volume residual tumours argues for abbreviated treatment intervals. In the 1970s (when the hypothesis was first advanced) haematopoietic support technology was rudimentary and a single cycle of high-dose therapy was as much as the majority of investigators were willing to attempt [47]. Thus, induction/consolidation was the most feasible adaptation of the model at that point in time. The introduction of peripheral blood progenitors, however, did facilitate the investigation of multicycle high-dose therapy at standard [48, 49], or abbreviated intervals [50–53]. It is against this historical and theoretical backdrop that we should consider the results of the first two randomised studies of high-dose chemotherapy in metastatic breast cancer.

Bezwoda and colleagues randomly assigned patients with chemotherapy-naive metastatic disease to receive either conventionally dosed mitoxantrone, vincristine and cyclophosphamide, or high-doses of cyclophosphamide, etoposide and mitoxantrone without induction therapy [54]. Patients who received the high-dose treatment had a significantly improved response and duration of survival. The study was relatively small and a disproportionate number of patients on the high-dose arm received tamoxifen after chemotherapy. In addition, patients in the low-dose arm had rather poor survival. However, interestingly, many of the patients in the high-dose arm were not hospitalised for complications of cytopenia, a finding that suggests that the high-dose regimen in this trial was less intensive than those used in other studies.

The study by Peters and colleagues represents a test of the classic induction/high-dose consolidation model in that patients with metastatic breast cancer who had achieved a complete response to conventionally dosed chemotherapy were randomised to undergo high-dose chemotherapy as immediate consolidation, or to receive no further treatment until they relapsed, when 'salvage' high-dose chemotherapy was applied [55]. The group that underwent immediate consolidation had a highly significant prolonged disease-free survival compared with those who were observed only, supporting the concept of 'late-intensification'. Paradoxically, the latter group of patients who underwent 'salvage' high-dose chemotherapy had a superior overall survival. While this apparently confusing observation will require explanation and confirmation, high-dose chemotherapy was, nevertheless, associated with a 5-year survival rate of approximately 25%. Further, the results of this study suggest that reconsideration of this therapy in relapsed metastatic disease may be necessary.

While these two studies confirm the results of the single-arm trials of high-dose chemotherapy and go some way

towards establishing its credibility, conventional chemotherapy has also improved in recent years and it is essential that the conventional arms of future confirmatory trials also be optimised. In one such planned initiative, the European Breast Cancer Dose-Intensity Study (EBDIS-I), patients will receive docetaxel and anthracycline-containing 'conventional' chemotherapy, followed by either CMF or two autograft-supported high-dose cycles. Future studies will probably address the merits of the various high-dose strategies and of graft engineering [56, 57]. The impact of high-dose chemotherapy may also be greater in the setting of high-risk stage II-III disease, where the tumour burden is many times smaller than it is in patients with clinically overt metastases. Promising results have been reported from single-arm studies [42, 58] and this approach is now the subject of large randomised trials in North America and Europe.

BIOLOGICAL THERAPIES

While biological therapies have become an accepted therapeutic modality in haematological malignancies, melanoma and renal cell cancer, they have until recently, had no established role in any of the common carcinomas. The recent demonstration that antibody therapy could reduce the frequency of relapses in patients with node-positive colorectal cancer has, however, renewed interest in this area [59].

Baselga and colleagues treated patients with metastatic disease whose cancer expressed the her-2-neu protein with an antibody that was directed against this antigen, and reported several clinical responses. Preclinical studies suggest that there may be synergistic cytotoxicity between this antibody and chemotherapeutic agents [60]. Kennedy and colleagues have investigated another novel biological approach: the induction of a syndrome of 'autologous graft versus host disease' as an adjunct therapy following high-dose chemotherapy [61]. Investigators in Memorial Sloan-Kettering have demonstrated substantial immunogenicity for a breast cancer vaccine [62]. Gene therapy approaches are also the subject of investigation [63].

SUMMARY

Several exciting advances have occurred recently in the treatment of metastatic breast cancer. The taxoids now have an established role in the treatment of this disease. The results of the first randomised trials of high-dose chemotherapy confirm both the high activity of this approach and the fact that a minority of patients achieve prolonged survival. Biological therapies remain investigational, but the results of an ongoing study may indicate a role for this modality in the future.

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