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EJC Supplements Vol. 4 No. 13 (2006) 6–11

EJC Supplements

www.ejconline.com

Interpreting metastatic breast cancer data in the latter half of this decade

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Abstract

The management of metastatic breast cancer has evolved considerably in the last 5–6 years and a variety of treatments have been shown to impact on the natural history of this disease over this period, with demonstration of survival prolongation justifiably generating considerable excitement. However, the question may be asked whether the success and clinical utility of novel therapies should be defined solely by this criterion. This paper will advance the view that several additional considerations should be weighed in the interpretation of data from randomised, controlled trials in determining a drug's clinical utility. The presence or absence of a survival advantage must be scrutinised in the context of the biological principles underpinning a drug's activity, the mix of patient and tumour characteristics in the population under study, the implications of 'cross-over', and the effect of other active therapies used upstream and downstream of the intervention under study, including the changing standards of adjuvant therapy. Lastly, the relative toxicity of regimens under comparison is particularly relevant to the feasibility of their wider application. In this report, each of these considerations is reviewed and their influence for trial design discussed.

Keywords: Metastatic breast cancer; Cross-over; Survival; Gompertzian growth kinetics; Adjuvant chemotherapy

1. Introduction

The central challenge to the development of new agents for the treatment of epithelial malignancies is the tendency of such tumours to acquire drug resistance through a variety of genetic and epigenetic mechanisms. In the case of women with advanced breast cancer, the probability of their disease manifesting drug resistance or degrading performance status or organ function to the point where treatment becomes impossible approaches unity, due to tumour phenotypic instability and cellular mass. Together with the kinetics of chemosensitive tumour cell repopulation rates, which follow Gomperzian growth curves after cytoreduction, these features of tumour biology render discrimination of therapeutic benefit through the razor of measurable survival extension extremely difficult [1] (Figure 1). For years it was a tenet of undergraduate teaching that the aim of treatment for metastatic breast cancer was palliative, a view which engendered critical uncertainty about the relative benefits of exhibiting drugs in simultaneous combination, as against single-agent regimens deployed sequentially [2].

The principal reason for exhibiting drugs in combination is now recognised as the pursuit of synergy, a term for many years used fairly loosely. But regardless of how stringently such preclinical phenomena may now be defined [3], there still remains significant doubt in the minds of many

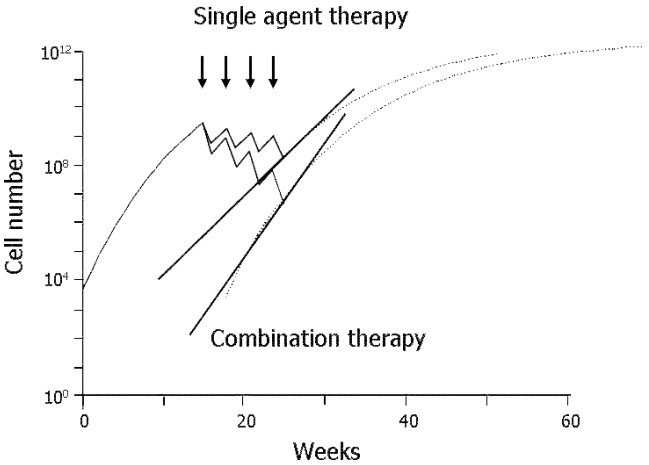

Fig. 1. Gompertzian growth kinetics and impact on survival with single-agent or combination chemotherapy. Adapted from [1].

clinicians about the relevance of such interactions in the clinic, particularly between cytotoxics. Historically, the rationale for combination therapy in epithelial tumours was rather less sophisticated, encouraged by the development of MOPP and CHOP in lymphoid malignancies, building on the lessons of anti-tuberculosis chemotherapy. However, in anti-cancer therapy, the discovery and development of drugs with novel mechanisms of action (the holy grail of drug development), has provided only modest non-cross-resistance. Furthermore, given their poor therapeutic index, any advantage in combining cytotoxics with different

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patterns of organ toxicity at individual doses below the maximum tolerated, has until recently seemed largely theoretical.

Combination therapy is the preferred way to evaluate the utility of a new agent in phase III trials since it lends itself to a reassuringly ethical approach in which patients on both arms of the trial receive a standard drug of proven efficacy up front. However, whilst trials of this design may offer elegant proof of concept, they do not necessarily define the optimal integration of a new drug into existing therapy. Nevertheless, whilst higher response rates (which imply potential for better palliation of disease-related symptoms) and prolonged disease-free survival (which indicates significant impact on disease natural history) are welcome indicators of a drug's potential, it is the repeated demonstration of survival advantage in properly powered and designed trials that has generated the most excitement in recent years. As a result, without much thought, survival improvement has become the endpoint that defines a drug's utility, and has become the leitmotif for a new era in breast cancer treatment. But is this view entirely justified, given the vagaries of the interplay of patient characteristics, tumour biology and mechanism of anticancer drug activity evident in clinical trial outcome? And if we adopt survival prolongation as a razor for licensing, or endorsement, do we risk discarding potentially useful drugs? Perhaps this consideration behoves both greater care in the analysis of clinical trials and a more sophisticated approach to trial design. This article will discuss some potential pitfalls in these processes and debate their importance.

2. Difficulties in balancing prognostic factors in trial design

The importance of balancing potentially confounding patient and tumour characteristics of prognostic importance by stratifying randomisation in phase III trials have been appreciated for many years [4]. However, the time from diagnosis to first metastatic relapse is often not considered in the design of randomised studies. It is, however, a very important prognostic factor, as shorter time-to-relapse is often associated with a worse prognosis. This association is clearly demonstrated in the study by Karrison and colleagues who performed a retrospective analysis of dormancy of breast cancer after mastectomy [5]. Long-term, follow-up data were examined from 529 patients who had undergone a radical mastectomy during 4 decades at the University of Chicago Hospitals. Patients whose disease had recurred within the first 5 years after their mastectomy had a significantly shorter post-recurrence survival time than those whose disease had recurred later (Table 1). The 5-year, post-recurrence survival rates were 6.9% for patients relapsing within 2 years and 11.6% for those relapsing within 2–5 years, compared with 32.4% for patients relapsing between 5–10 years.

Table 1
Distribution of survival times (stratified by time to recurrence) following recurrences in 529 patients who had undergone a radical mastectomy [5]

Group[a]	Numbers at risk			
	0 years	2 years	5 years	10 years
1	232	52	16	6
2	179	74	20	4
3	69	38	19	7
4	31	15	5	0
5	18	6	3	1

[a] Group 1, ⩽2 years; group 2, >2–5 years; group 3, >5–10 years; group 4, >10–15 years; group 5, >15 years. Reproduced by permission of Oxford University Press.

However, despite incorporating this and other prognostic factors into their stratification design, Tannock and colleagues have described encountering chance imbalance in tumour biology across treatment groups – not withstanding standard randomisation procedures, which confounded trial outcome – by influencing the outcome of interim analysis [6]. In a study comparing two dose levels of cyclophosphamide, methotrexate, and fluorouracil, accrual was ceased after second interim analysis, which showed significantly longer survival in the group receiving higher-dose chemotherapy. After the trial closed they belatedly discerned an unexpected imbalance in tumour biology, with a median 1.4 years' relapse to randomisation for low-dose and 2.1 years for higher dose treatment groups. This occurred despite trial entry criteria excluding all patients with rapidly progressive visceral disease, and randomisation stratified by disease site, previous hormonal therapy or not, and time from primary surgery to first relapse. To the authors, these improbable events underscored the importance of confirmatory trials, an endeavour which requires timely planning to assure ambient equipoise and to avoid recruitment to a second trial falling victim to clinical prejudice.

Scrutiny of more modern studies provides additional evidence of the impact of patient selection and patient status on overall survival. Interim analysis of a phase III study evaluating gemcitabine in combination with paclitaxel in relation to paclitaxel alone shows a survival advantage for the combination at 42 months' follow-up [7]. However, representation of the data as Kaplan–Meier curves shows considerable congruence of the plots during the first 6 months of the study, with divergence between 6–36 months and convergence again at 36–42 months. The lack of survival advantage in the first 6 months may be a function of the refractory nature of malignant disease in patients with poor performance status, high tumour volume, rapidly progressive visceral metastases and poor oestrogen-receptor (ER) status. At the end of the 42 months, the population may be dominated by patients harbouring relatively indolent well-differentiated tumours with high levels of ER- and progesterone receptors, and at this point,

the impact of hormonal therapies may have a greater influence, thus obscuring any advantage for combination chemotherapy.

This outcome has occurred despite the treatment groups being balanced by randomisation and also by stratification for key prognostic factors. Multivariate analysis for factors significantly associated with interim overall survival included performance status (Karnofsky score $\geqslant$90), treatment group allocation, time from diagnosis, and number of tumour sites. Prognostic factors that were not significant in this trial included the presence of visceral disease, prior therapy, receptor status, and age. It is possible that the follow-up period may have been too short for receptor status to achieve statistical significance. It is also possible that extended follow up will only dilute the therapeutic benefit evident on interim analyses. These considerations argue for over-engineered power calculations for trials with traditional entry criteria or more restrictive entry criteria for chemotherapy trials of this design.

3. Biological principles of drug activity

Identification of the appropriate patient population is vital in demonstrating the activity of a novel therapy. This is clearly shown by the pivotal trastuzumab (Herceptin®) combination therapy trial [8], in which the survival advantage with therapy would not have been demonstrated had trastuzumab been evaluated in an unselected group of patients. The usefulness of a more conservative view of drug-receptor interactions in anti-neoplastic therapy has recently been discussed by Sledge. A broader appreciation of drug targeting and a move away from the intellectually sterile concept of conventional cytotoxics as 'blunderbuss' therapy may be crucial to understanding better how to identify and target patients with potentially responsive tumours. For example, gemcitabine is a pro-drug that is activated by deoxycytidine kinase, the expression of which may be an important factor for predicting its success; furthermore, as an anti-metabolite it seems plausible that gemcitabine might selectively affect tumours containing a higher proportion of proliferating cells.

4. The influence of cross-over; limitations of trials with cross-over designs

Cross-over after progression has been raised as a concern in several trials that have typically compared a combination of research drug and standard drug with the standard single-agent therapy and failed to demonstrate improved survival for the combination. This failure has been attributed to patients in the research arm being crossed over to the research drug on progression, often on compassionate grounds. Conversely, many commentators have noted the absence of cross-over in several positive combination versus single-agent studies and have suggested that the favourable outcome may have reflected the fact that the research drug was not made available later. However, this hypothesis has never been tested directly in a randomised trial of cross-over versus none (and is unlikely to be!).

For many, the trial that has come closest to addressing this issue is a three-way phase III comparison of single-agent doxorubicin 60 mg/m^2, versus single-agent paclitaxel 175 mg/m^2 versus the combination of doxorubicin and paclitaxel (50/150 mg/m^2) as first-line therapy for metastatic breast cancer [9]. Cross-over was recommended in the protocol for patients treated in the single-agent treatment groups. The trial failed to demonstrate any significant survival advantage for the combination although this was perhaps not surprising, as the study was powered only to discriminate differences in response rates and time to progression. Furthermore, in the single-agent arms of the trial, only 50% of patients in each group switched to the alternate therapy, of which only 20% obtained objective responses, the vast majority of these being partial. If one accepts that, outside the context of maintenance studies, only complete responses impact on the natural history of the disease, whereas partial response provides only scope for palliation, the influence of cross-over as the explanation for failure of the combination to extend survival seems implausible.

The results of a recent audit conducted at the West Midlands Cancer Intelligence Unit evaluated 100 consecutive deaths from metastatic breast cancer and confirm the limited scope for cross-over in influencing outcome. We reviewed data from one teaching hospital and two district general hospitals and recorded the number of chemotherapy regimens received by each patient prior to death. In this population, one-third of the patients were deemed too old and too frail to receive any chemotherapy. Sixty-six percent of patients received first-line therapy and by a process of summation, it was possible to assess the attrition rates between first and second, second and third, and third and fourth line chemotherapy and so on. These losses were quantitatively similar to those of the Sledge study, with 50% or more being lost at each step, implying many patients whose disease progressed or relapsed were judged too sick to receive additional chemotherapy, and the opportunity for further treatment was therefore lost. Logically then, were there scientific interest in comparing combination versus sequential single-agent strategies, a better trial design would necessarily feature a consolidation strategy, in which the new drug was evaluated either ahead of relapse or as salvage therapy in those whose disease progressed on therapy. This model would have one other important advantage; subsequent therapy, off protocol, would be balanced in both arms. Sledge's study, for example, contains no data about treatment subsequently received by patients initially randomised to the combination arm. At the time the trial was conducted, useful options in this context were limited; that may not be the current case. Lastly, in keeping with

these conjectures and observations, analysis of the impact of cross-over in studies of trastuzumab, have not shown significant effect [8].

5. The influence of changing standards of adjuvant therapy

The last 5 years has seen a higher proportion of patients receive adjuvant chemotherapy than ever before. Furthermore, this change has also been associated with the use of both more complex and more intense chemotherapy regimens. This has had the effect of narrowing the treatment options for patients relapsing later with metastatic disease, particularly in respect of their candidacy for taxanes, which have become increasingly widely used in the adjuvant context. This has resulted in drugs such as capecitabine, gemcitabine, vinorelbine, or platinum becoming options for first-line therapy for metastatic disease. This scenario is exemplified by those patients who relapsed early after treatment on the research arm of the tAnGo trial, and were assumed to have disease resistant to epirubicin, cyclophosphamide, paclitaxel and gemcitabine [10].

As a result of the greater complexity and intensity of modern adjuvant regimens, new drugs may manifest lower response rates in phase II trials conducted in patients who subsequently relapse; lower levels of activity may therefore need to be accepted as sufficient to justify their further development. And as a corollary, response rates recorded in older phase II studies may now provide misleading reference points for newer drugs. Single-arm phase II studies may no longer provide intuitively appreciable evidence of a new drug's clinical activity. Not only may a new generation of computed tomography scanners with higher definition effectively reduce the numbers of patients declared as enjoying a complete response, but objective response rates of potentially useful drugs evaluated in these conditions may be lower than older conventional thresholds for justifiable scientific interest. Randomised phase II studies may therefore offer a useful way forwards; whilst not powered to compare the activity of a novel agent against a conventional therapy, this methodology is an established means of using an established drug such as capecitabine in a reference arm to deduce from its activity the impact of otherwise occult patient-selection factors on the activity of the agent under research. In this instance, any reduction in expected activity in the reference arm may indirectly quantify the magnitude of the molecular challenge facing a new agent in the research arm [11].

6. Relative toxicity of regimens under comparison

The relative toxicity of regimens must be considered when assessing their clinical advantage, as this may have implications for their wider feasibility. In a randomised, phase III study of docetaxel 100 mg/m^2 versus paclitaxel 175 mg/m^2 in patients with metastatic breast cancer [12], there was a modest survival advantage for docetaxel. However, docetaxel and paclitaxel were not equitoxic; febrile neutropaenia, for example, occurred in 15% of patients in the docetaxel arm compared with only 2% of those in the paclitaxel arm, an approximately seven-fold increase. It is therefore important to weigh the survival advantage of docetaxel against its increased toxicity over paclitaxel. Similar concerns apply to the combination of capecitabine and docetaxel, which showed a survival advantage over docetaxel alone [13].

7. Endpoints

The selection of endpoints is crucial in determining the utility of novel therapies, and relying on a demonstration of improvement in overall survival may not reflect the true activity of a compound. Prolonged follow-up may also reveal unexpected changes in outcome relating to the efficacy of a novel therapy. In the phase III Eastern Cooperative Oncology Group E2100 trial, in which first-line treatment with paclitaxel and bevacizumab was compared with paclitaxel alone in patients with metastatic breast cancer, early follow-up results showed that the addition of bevacizumab to paclitaxel significantly prolonged progression-free survival (Figure 2A) [14]. However, this very positive early finding

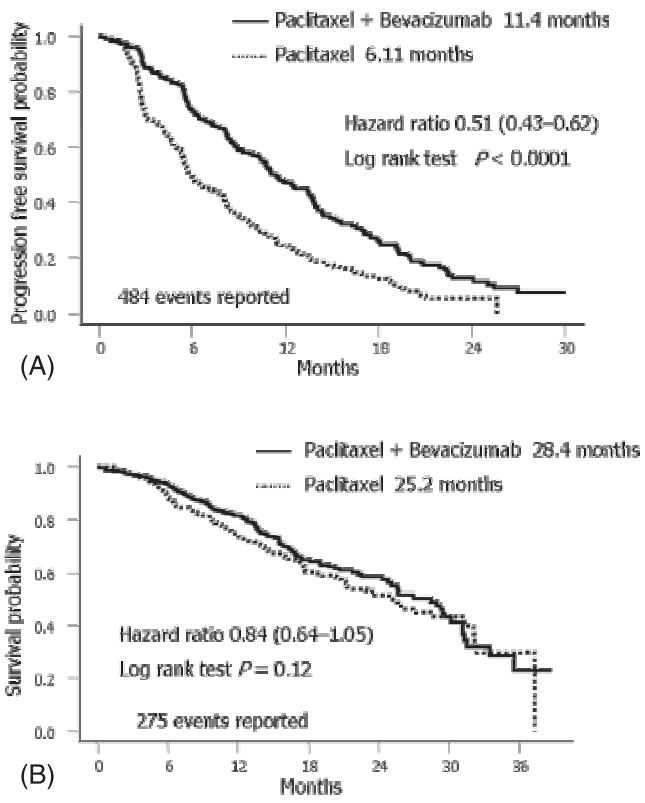

Fig. 2. Study of paclitaxel and bevacizumab versus paclitaxel: (A) progression-free survival [14] and (B) overall survival [15].

did not translate into subsequent positive results for overall survival (Figure 2B) [15]. The reason for this disparity is not at all clear, but the explanation may lie in the novel mechanism of action of this compound. Plausibly, those tumours exposed to bevacizumab in the research arm, and whose progression is at first slowed on this therapy, may experience some 'rebound' angiogenesis after progression, following withdrawal of therapy. Such patients may then experience accelerated rates of tumour growth, which depart from the classical kinetics of the Gomperzian curve. This begs important questions about the potential importance of scheduling or duration of experimental treatment in clinical trials; whilst we have only recently begun to grapple with the vagaries of fixed duration treatment for 6 cycles (as typified in UK standard practice) as opposed to treatment until disease progression (as typified in the USA), very little attempt has been made to evaluate the influence of treatment beyond progression, beyond one or two specific treatment scenarios where there is a *prima facie* hypothesis to test, for example, in the evaluation of fulvestrant (Faslodex®) with or without an aromatase inhibitor after disease progression on an aromatase inhibitor, which was the principal question addressed by the UK's SoPHEA trial (principal investigator Stephen Johnson). The effect of fulvestrant may depend on persistent oestrogen deprivation. In the realms of chemotherapy trials, treatment until disease progression is feasible only if the cumulative toxicity of the drug is exceptionally modest, and the drug is easy to administer and ideally formulated for oral absorption. With trastuzumab, the question is different again, relating to whether continuation of treatment beyond progression brings additional advantage from synergistic activity in combination with subsequently exhibited cytotoxics, such as vinorelbine (Navelbine®).

8. Novel agents

An example of a novel drug that is in early development for the treatment of solid epithelial tumours is enzastaurin. Enzastaurin is an oral serine-threonine kinase inhibitor that is designed to suppress tumour growth through multiple mechanisms. It primarily inhibits signalling through both the protein kinase C-β and P13K/AKT pathways. Preclinical data indicate that it may reduce cell proliferation, increase apoptosis, and inhibit angiogenesis [16]. It has demonstrated preliminary activity in glioblastoma multiforme [17] and B-cell lymphoma [18] and shows promise for consolidation regimens and maintenance therapy. For the acceptance of this drug in targeted indications, including its use in the treatment of metastatic breast cancer, the design of clinical trials and interpretation of data will be crucial.

9. Conclusions

The results of all randomised clinical trials require careful scrutiny as a failure to demonstrate an advantage in overall survival may not necessarily indicate a lack of superior efficacy in terms of time-to-disease progression. Cross-over effects may be unproven, and the possibility of underpowered studies or the impact of Gompertzian growth kinetics should be considered in the interpretation of data. It may be prudent to restrict and select the populations in clinical trials of cytotoxics using conventional tumour characterisation in order to define the group of patients likely to benefit. For newer targeted agents, trial populations should be suitably enriched; additionally, trial design and endpoints should reflect the pharmacology and biological activity of the drug under investigation. Other difficulties may then ensue; not only is metastatic disease becoming slowly less frequent, but trials will selectively recruit form particular subsets of patients, and thus render timely trial recruitment more difficult.

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