Anti-Cancer Drugs 1995, **6**, Suppl 5, pp. 17–27

The importance of dose and schedule in cancer chemotherapy: breast cancer

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For a variety of reasons, sociopolitical as well as biological, breast cancer therapy has become an area of great public and professional interest over the last decade. Studies in the US have focused on intensive and high-dose chemotherapy, both in advanced and in high-risk adjuvant settings. In the UK more attention has been paid to primary medical therapy and lessons have been learned on the value of scheduling as well as dose. With peripheral blood stem cell transplantation technology established we are now in a position to examine intensive chemotherapy in high-risk and in advanced disease and must take the opportunity to establish its relative benefit in randomised clinical trials.

Introduction

Breast cancer is the most common non-cutaneous malignancy affecting women in the Western world and is the most frequent cause of cancer death among them. It is the most common cause of death from all causes in women in the fifth decade of life. In the UK there are annually approximately 25,000 new cases of breast cancer and nearly 16,000 deaths. Because of the long natural history of the disease in many cases, the estimated prevalence in the UK is around 110,000 cases, far outnumbering any other of the common cancers.

Most patients present with what appears to be localised disease and despite careful clinical, biochemical and radiological assessment show no evidence of secondary tumours. However many of these women will ultimately die from breast cancer which has metastasised, and the currently accepted paradigm is that breast cancer presents as a systemic disease in many cases with the secondary disease being present as undetectable micrometastases. This concept has important implications for increasing curability by elimination of the putative microscopic secondary disease at the time of initial presentation.

The most important prognostic factor for patients who present with apparently localised disease is the status of the axillary lymph nodes. If the nodes are not involved, local therapy is curative in approximately 70% or more of cases, but for patients with lymph node metastases the prognosis is poor and it deteriorates progressively as the node numbers increase.[1] Probably between 60% and 80% of women with four or more lymph nodes will eventually develop overt metastases.

In 1969 Cooper and colleagues, in a paper never published in more than abstract form, showed that chemotherapy could also profoundly influence the outcome of advanced breast cancer.[2] In the subsequent 25 years a variety of clinical trials were performed which failed to show a major benefit from chemotherapy for advanced disease in terms of survival gain. Even used in the adjuvant setting, chemotherapy did not show clear survival gains, with different trials showing diverse results. Eventually the overview analyses combining the results of individual randomised trials, at the last analysis including an aggregate of some 75,000 women, clearly showed for the first time that adjuvant systemic chemotherapy does reduce the death rate from breast cancer up to 10 years following treatment. It is now accepted that combination chemotherapy in standard doses must work by destroying the hypothetical micrometastatic disease.[3,4]

Management of hormone-insensitive advanced disease has long been an area of controversy, with a balance being sought between optimising cancer control against chemotherapy side effects. Recent developments in medical technology have encouraged a limited amount of experimentation with infusional chemotherapy and exploiting the prop-

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Table 1. Toxicities and adverse events related to 5-FU infusion

Ref.	No. of pts	Toxicity (% of evaluable patients)						
		Mucositis	PPE *	Diarrhoea	Nausea / vomiting	Catheter-related problems	Marrow suppression	Ataxia
7	25	16	36	8	3	0	0	0
8	24	25	13	17	0	0	17	0
10	28	36	29	11	0	21	14	11
11	32	38	21	0	3	6	19	0
12	10	40	10	30	30	0	0	10
15	27	30	24	24	0	0	0	0
13	23	13	0	0	0	9	0	0

* Palmar–plantar erythrodysaesthesia.

erties of growth factors to enhance the anticancer effect by increasing drug doses.

Optimal scheduling of chemotherapy in advanced breast cancer

The evidence in favour of the importance of drug scheduling in clinical studies of breast cancer is limited to the experience of 5-fluorouracil (5-FU) and doxorubicin/epirubicin. The 5-FU experience is interesting however because of the time it has taken to evolve schedule optimisation.[5–19] The drug has been around for nearly 40 years but it is only in the last decade, and with serious attention only in the last 5 years, that studies have addressed the question of optimal scheduling.[14] Undoubtedly part of the explanation is the technology advance that has seen the introduction of long-lasting intravenous lines and especially the availability of reliable, relatively inexpensive, lightweight portable infusion pumps.

5-FU infusion can be given both as a single agent and as a component of combination chemotherapy with the expectation of producing high response rates and well tolerated toxicity (Table 1). The evidence for schedule dependency is mainly based on clinical experience of breast cancer, although studies in gastrointestinal cancer provide further support.[19] As a single agent, infusional 5-FU produces a response rate of about 30%–35% in previously treated patients (Table 2), including those exposed to prior bolus 5-FU.[13] This is at a dose level of 200–300 mg/m^2 daily continuous infusion. The actual daily dose in this range appears not to be critical, though formal randomised trials to address this are lacking.[13] In combination chemotherapy it can be given at 200 mg/m^2 daily without apparent penalty in terms of toxicity, and the overall activity is higher again, depending on the patient population and the added drugs.[20–30] Thus, when combined with cyclophosphamide and methotrexate in a design based on the 3-weekly CMF regimen ('CMF-inf') it produces a response rate of around 50% in a previously treated population,[20] whereas when combined with epirubicin and cisplatinum, the latter two drugs again given by bolus injection 3-weekly, the response rate in previously untreated disease is around 95%![30] The increased activity may be due in part simply to the increase in total dose intensity of the 5-FU which, at 1400 mg/m^2 per week, is escalated in effect by around 5- to 7-fold above conventional doses. However, whether the infusion needs to be prolonged more than a few days is uncertain.[31]

Schedule variation studies have also been examined for doxorubicin to look at weekly lower-dose doxorubicin as against 3-weekly scheduling, the total intensity being equivalent.[32] The overall impression is that there is no net benefit from weekly scheduling, though there may be an advantage for patients with impaired hepatic function in giving lower weekly doses.[29] The theoretical benefit for the heart with a lower AUC though detectable physiologically is not clinically manifest.[32] However, again in combination with continuous 5-FU, weekly doxorubicin, AcF, may be an attractive scheduling option for patients with a weekly commitment to the clinic in whom careful monitoring of response and toxicity is important, particularly for those with major organ dysfunction. This approach has proved to be effective in a bad-risk group of

Table 2. Range of doses of 5-FU infusion and response rate in clinical studies

Ref.	Range of doses of 5-FU infusion ($mg/m^2/day$)	No. of pts	Response rate (%)
7	200–300	25	32
8	300–500	6	4
9	250–300	25	28
10	175–250	28	53
11	150–250	32	16
12	200–300	10	30
15	175–300	27	12
13	200	23	35

metastatic disease and has produced response rates, allowing for the patient population, similar to that seen with ECF at around 85%.[29] The interesting observation in all these studies is that despite an increase in dose intensity of significant proportions, the toxicity increment is small and manageable for most patients, and seems to depend almost entirely on the added drugs in the schedule. Thus 5-FU alone produces few or no toxic symptoms, CMF-inf produces side effects comparable with those of CMF 3-weekly bolus and ECF/AcF produce acceptable toxicity but at a higher level due to the anthracycline (and platinum). One caveat concerning toxicity is the observation of a tendency to cause palmar and plantar skin toxicity which can be sufficiently severe to necessitate temporary interruption in the treatment. Oral and gastrointestinal mucositis (diarrhoea) can also occasionally be problematic. The overall activity and tolerance however have made infusional regimens attractive options and they are being adopted with some enthusiasm in the preoperative treatment of breast cancer, at least in comparative trials against standard bolus regimens.

There are some observations on the optimisation of scheduling for other agents, such as cyclophosphamide, which is routinely used at conventional and at high doses in breast cancer (see also Ranson M, Thatcher N, pp. 53–63, this supplement). In one area of adjuvant treatment the question of cyclophosphamide dose/schedule has been addressed in a randomised trial comparing 'classical' against 3-weekly intravenous CMF.[33] The EORTC trial showed a statistically significant advantage for the oral higher-intensity schedule in the treatment of advanced disease. However this was not a pure test of cyclophosphamide scheduling as the other drugs were also varied between the two arms.

Dose intensity: laboratory and theoretical models

The relationship between drug dose and cell kill of cancer cell lines or human tumour xenografts in experimental models follows a complex sigmoid curve. There is at lowest drug doses a threshold to be reached to achieve any effect (the lag phase), then a linear phase and finally a plateau. The tumour response during the linear phase, especially using alkylating agents, is steep and logarithmic.[34–40] Reducing doses in this phase will result in failure to eradicate the cancer. In animal models this may not be reflected in the complete response (CR) pattern but will emerge as ultimate relapse in place of cure. These results were observed in a series of experiments performed by Skipper and colleagues using the Ridgeway osteosarcoma tumour in rodents.[40] Thus the two-drug combination of cyclophosphamide and melphalan was capable of producing 100% cures at one dose level, whereas a reduction to an average dose of 60% reduced the cure rate to 60% without affecting the immediate CR rate which remained at 100%. However reducing dose to around 30% cut the CR rate to 10% with 0% cures. These observations are not lost on the clinician who recognises a clear enough relationship in similar proportions between CR rate and cure, the high CR rate predicting cure in testicular cancer, intermediate rates of each for lymphomas and the low CR rate of around 10% with no cure seen for conventional chemotherapy in the majority of 'sensitive' solid cancers such as advanced breast cancer. A further point of importance translating into clinical studies is the observation *in vitro* of the occurrence of spontaneous mutations at around 1 per 10^6 to 1 per 10^7 cells.[38] This makes a case for the use of more than one cytotoxic agent with a different mode of action to minimise the risk of somatic mutation-associated cross-resistance. The interest in exploiting high-dose chemotherapy therefore emanates from a variety of clinical and laboratory experiments.

The classical model for demonstrating a dose–response effect from chemotherapy was developed by Skipper and Schabel using the murine L1210 leukaemia cell line. This was reproduced when human cell lines became available, and results from studies on tumour cell lines including the MCF 7 breast cancer cell line mimic the results of the L1210

leukaemic mode. Thus Frei and colleagues have shown that *in vitro* many alkylating agents when escalated linearly demonstrate a logarithmic cell kill against MCF 7.[41,42] These results are often quoted as the laboratory rationale that underpins the logic of true dose intensification in the adjuvant setting where micrometastases are thought to be the closest clinical analogue of the *in vitro* experiment. It follows that increasing the cytotoxic drug dose in a sensitive system will increase the cure rate and demonstrable logarithmic increments in cell kill are observed after doubling the dose. Finally, *in vitro*, breast cancer cell lines like other cancer cell lines routinely show a lack of cross-resistance between alkylating agents, justifying their combination, especially where, for most alkylating agents, the second-organ toxicities differ and the main toxicity remains bone marrow.

Clinical studies of intensity within the standard range: adjuvant chemotherapy

With the recognition that therapy could affect outcome, clinicians immediately began to address the question of a dose effect, at first retrospectively. Hryniuk and colleagues in a flawed but very influential review of published trials, and Bonadonna in a retrospective analysis of his adjuvant CMF trial, claimed to show a relationship between dose applied and survival.[43,44] These analyses seemed to support the interpretation of the laboratory studies by Skipper, Frei and colleagues. Subsequently, however, dose–response studies performed in randomised clinical trials have shown somewhat conflicting results.

It is very difficult to mimic the laboratory experiments in the clinic. Thus Hryniuk's retrospective dose-intensity analysis of several trials, both in adjuvant and advanced breast cancer, estimated the delivered dose per unit time (mg per m^2 per week) for each drug in a combination chemotherapy schedule and compared that dose rate against an arbitrary standard dose intensity.[45] Unfortunately, due to variations in schedule design, many of the chosen examples studied either had extra drugs added or drugs excluded. Also assumptions not justified by our knowledge of drug action nor by observed effects in the laboratory (for example, unlike alkylating agents, antimetabolites show far less or no dose–response effects against cell-lines) gave average dose intensity for a given combination regimen that gave equal weight to the impact of halving cyclophosphamide as halving methotrexate. Significantly, no regard was paid to potentially important schedule effects, probably very important for agents such as 5-FU.

Despite theoretical problems, when this sort of analysis was applied to breast cancer trials, the correlation between calculated relative dose intensity and outcome was impressive, providing support for the idea that actual dose delivered impacts on the response rate and survival of this relatively chemosensitive cancer.

A critical rebuttal of the Hryniuk and Bonadonna analyses however, by Gelman and Henderson, demands caution in interpretation of such retrospective analyses.[3]

Studies of dose variations: metastatic disease

A relationship between dose, schedule and outcome might be expected to be more important in the adjuvant setting than in advanced disease where for a number of reasons, mainly to do with drug access and tumour biology, the clinical equivalent of the cell-line/drug log–linear dose relationship is much less likely to obtain in the latter as compared to adjuvant therapy. Whilst trials have been conducted in adjuvant therapy of breast cancer, the more difficult and unsatisfactory field of treatment has been in the management of metastatic disease with chemotherapy. Currently the disease is regarded as a uniformally fatal condition, albeit with a widely variable course and speed of progression, and is treated with chemotherapy therefore in a palliative mode. It is nevertheless a relatively responsive tumour and in a large unselected series of metastatic breast cancer patients reviewed by Eddy the overall response rate from chemotherapy is between 13% and 83% with complete remissions occurring in less than 10%, mostly of limited duration between 3 and 17.5 months.[46] Chemotherapy does however probably—although not certainly—improve the survival of breast cancer by a few months, and the overall survival is poor at between 18 and 24 months from presentation with secondary disease. Limited to the cases where hormonal therapy has failed or is deemed inappropriate, survival from commencement of chemotherapy is much poorer, at around 12 months according to a large series of patients from an audit at Guy's Hospital and Edinburgh.[47,48]

Many patients who commence chemotherapy have a relatively short survival, either because they have tumours with a more aggressive natural history or because by the time chemotherapy is commen-

Table 3. Randomised trials of dose in patients

Number in	Treatment	RDI	Response rate +	Survival
[1] 60–283	CMF or FAC/FEC	1–3	3/6 sign.	2/4 sign.
[2] 23–202	3 A, 2 E, 2 CP, 1 CMF	1.3–2	1/8 sign.	1/3 sign.*

[1] No prior chemo, [2] prior chemo. RDI = Relative dose intensity vs 'standard'. C = Cyclophosphamide, T = thiotepa, L = melphalan, P = cis-platinum. CMF = cyclophosphamide, methotrexate, 5-FU; FAC = 5-FU, adriamycin, cyclophosphamide; FEC = 5-FU, epirubicin, cyclophosphamide. + In 12/14 the response rate was clearly higher in the higher-dose arm. * In one trial survival was significantly *poorer* in the higher-dose arm. Adapted with permission from Antmann K. Dose-intensive chemotherapy in breast cancer. In: Armitage J, Antmann K, eds. *High Dose Cancer Therapy Pharmacology, Haemopoietins, Stem Cells*. Baltimore: Williams & Wilkins 1992.

ced they have already failed either one or more endocrine manoeuvres. The main aims of chemotherapy therefore for metastatic disease are to maintain or restore the quality of life following improvement of cancer symptoms balanced against the side effects of chemotherapy. This is essentially an area of trying to improve the therapeutic index of drugs.

To improve the present results of chemotherapy new potent drugs need to be developed or, in palliative designs, drugs with a better therapeutic index. A further option is to experiment with dose intensification in an effort to improve response rate and disease control and to extend survival within the limits of accepted tolerability. Amongst these new approaches, high-dose chemotherapy, as in the adjuvant situation, has been made possible—first by the introduction of autologous bone marrow transplantation supported by colony-stimulating factor (CSF) therapy and more recently by the use of CSFs to develop stem-cell supported dose intensification.

Is there any evidence from studies of dose intensity within the standard range that dose intensification might usefully be examined in metastatic breast cancer? Unfortunately, despite the positive interpretation of retrospective data by Hryniuk, the results of subsequent prospective randomised trials have been conflicting.[49] The data are summarised in Table 3. The most positive interpretation of these outcomes may be summarised as follows:

(1) The studies are all on a small scale and small advantages are likely to be missed.
(2) Results in metastatic disease are compromised by the problems of patient fitness, drug access, prior chemotherapy, including adjuvant therapy inducing resistance.
(3) Metastatic tumour cell growth characteristics which obey Gompertzian rules of a falling growth fraction are inherently less responsive and, in contrast to the adjuvant micrometastatic situation, do not show log–linear kill.
(4) Compared against dose ranges observed and attainable in the laboratory, the dose range within the standard clinical schedules is unrealistically small and unlikely to show important effects.
(5) As previously argued, many of the drugs used to treat breast cancer do not exhibit clear dose–response relationships even in the idealised conditions of the *in vitro* experiment.
(6) In published data few papers discuss the doses of drug given, as opposed to intended doses.
(7) It is highly probable that pharmacological effects produce important variability in the actual level of drug present, regardless of the received dose (see also Ranson M, Thatcher N, pp. 53–63, this supplement).
(8) In nearly all advanced disease and adjuvant studies the question being addressed within the standard dose range was 'can we reduce dose safely?'

These rationalisations, coupled with encouraging experience of tolerance and safety from using dose-intensive regimens in leukaemia and lymphoma treatment, led many investigators to conclude that the results of standard dose chemotherapy in metastatic breast cancer at least did not disprove a dose–response effect and that the data, although flawed, could in some studies be seen to indicate a slight association between dose and positive outcome, even in terms of quality of life![50] Again a note of uncertainty in the interpretation is implied by the possibility that in the lower-intensity arm of the trial quoted the dose was below an acceptable 'threshold' level for useful effect, so was not a true test of dose intensity as many would interpret it.

With the gradual acquisition of skill in managing complications of marrow suppression and the availability of new cytokines, many have concluded that the way to test the concept of dose intensity fairly to match the laboratory results was to resort to

autologous marrow and more recently peripheral blood progenitor cell support, escalating alkylating agents by 5- to 10-fold above standard doses.

Adjuvant high-dose chemotherapy

Experimental models suggest an invariable and inverse relationship between size of tumour and curability with cytotoxic agents. Thus chemotherapy which can produce substantial but non-eradicative cytoreduction in patients with overt metastases might nevertheless cure patients at an earlier stage harbouring a far smaller tumour burden. Clinical research seems to confirm these predictions since conventional-dose chemotherapy reduces relapse and prolongs survival in stage II disease far more impressively than in stage IV disease. However the results of adjuvant therapy are still unsatisfactory, particularly for patients with extensive axillary lymph node involvement. A lot of work has been conducted looking at various pathological and biological parameters predicting outcome.[51] However, there is still no individual feature which matches the information available from simply obtaining and counting the number of pathologically involved lymph nodes in the axilla at the time of primary surgery. Based on this we have a very good definition of relapse rates and survival in relation to node number and as a result a series of survival curves may be plotted against nodal status. No node-positive groups achieve better than 80% survival at 5 years but the worst groups (particularly those with more than 10 lymph nodes involved) show completely inadequate survival (< 50%) at 5 years.

The overview analysis of adjuvant therapy of breast cancer points to benefit from both endocrine therapy and chemotherapy. There is still a debate as to whether chemotherapy exerts its benefit for the premenopausal patients through secondary ovarian suppression but only one trial has ever directly addressed this question. The Scottish Group together with Guy's Hospital tested ovarian ablation against chemotherapy and the results published in the *Lancet* in 1993 suggested an equivalent effect with no discernable overall benefit for one or the other treatment.[52] Interestingly however a subgroup analysis according to oestrogen receptor status fitted the hypothesis exactly that patients with oestrogen receptor positive tumours gained more from ovarian suppression whereas those with oestrogen receptor negative tumours gained benefit from chemotherapy. This suggests that biologically separate subgroups require tailored adjuvant therapy.

Within clinical research, the partial success of adjuvant chemotherapy in the treatment of breast cancer together with clinically meaningful dose–response effects in advanced disease provides a clinical rationale for studying very-high dose chemotherapy in patients with a high risk in early stage disease. Two interesting studies show encouraging preliminary results in single-arm studies of high-dose chemotherapy in patients with breast cancer involving 10 or more axillary lymph nodes.

Peters treated patients with at least 10 positive lymph nodes with a regimen comprising cyclophosphamide, adriamycin, 5-FU over four successive conventional courses followed by a single consolidation course comprising high-dose carmustine (BCNU), cyclophosphamide and cisplatinum (the CBP regimen).[53] This had been developed from the experience of treating metastatic breast cancer with a different induction but similar high-dose regimen producing a high overall response rate and an impressive 'tail' on the survival curve, with some patients with metastatic disease going into unmaintained remission beyond 10 years. In the adjuvant trial, all patients received autologous bone marrow rescue (ABMR) and in later recruits ABMR was supplemented by granulocyte-colony stimulating factor (G-CSF) mobilised peripheral blood progenitor cells (PBPC). With a median follow-up of 3.3 years, 72% of patients remained free of relapse. Compared against this matched controls from the Cancer and Leukaemic Group B had relapse-free survival at 3.3 years for around 35%. Interestingly many of the relapses which occurred in Peters' study were locoregional and affected patients who were recruited prior to the institution of a policy of routine chest wall irradiation. However randomised trials have now been commenced on the background of encouraging outcomes from phase II trials whether the outcomes have been compared against historical controls.

In a further development of intensive chemotherapy, Gianni and colleagues examined a sequence of doxorubicin followed by high doses of cyclophosphamide, methotrexate, cisplatin and melphalan.[54] PBPCs were harvested following the cyclophosphamide course to rescue the melphalan high-dose therapy. Relapse-free survival at 5 years in this group of patients with at least 10 positive lymph nodes was 50%—again well above what would be predicted for this high-risk group of patients. Thus the data from both Duke University and Milan indicate very high relapse-free survival rates at 3 and 5 years which are clearly superior to those of 'matched' controls.

However these preliminary study results have not yet been substantiated. Prospective randomised trials are therefore required. The outcomes in terms of survival from systemic therapy with standard dose of chemotherapy in high-risk (multiple node-positive) adjuvant disease are simply too poor not to test such promising approaches. The safety factors involved have changed the applicability of high-dose therapy such that whereas 10 years ago up to 25% of patients were dying from complications of dose intensification, the figures are now well under 5% and possibly under 3%.[55] The result is that at least four European trials have commenced or are about to commence testing dose intensification and one very large trial is further ahead in North America. Within the next three to five years we will begin to get clear indications as to whether there is true benefit from this approach or not.

Since the pragmatic experiments with ABMR at the beginning of the 1980s, the area of dose intensification research in the clinic has become much more widely practised, particularly for the haematological malignancies. Since then we have collectively learned lessons about lethal complications including 'second-organ toxicity'. With increasing confidence in controlling complications of therapy, clinicians are now beginning to discover the potential benefits for this sort of approach in chemosensitive solid cancers, including breast cancer.[56,57]

The evidence in favour of micrometastases being a common problem in 'localised' breast cancer is thus overwhelming and is substantiated by the ongoing studies of immuno microdetection with antiepithelial monoclonal antibodies and by some investigators' ability to culture tumour cells from bone marrow.[56–61] These studies indicate an increasing level of risk of marrow involvement as the risk factors rise in relation to the primary tumour. This means that between 30% and 50% of bone marrows may have detectable disease, depending on the clinical stage of the tumour at presentation. Currently studies are underway to determine the importance of marrow or PBPC contamination by tumour and methods to deplete or eliminate the tumour population, either by 'negative' selection with drug or antibody against tumour or alternatively by positive selection of the progenitor cells with antibody to the CD34 antigen.[58]

High-dose chemotherapy in metastatic disease

The initial studies of very-high dose chemotherapy in advanced breast cancer were part of a programme of testing the concept of high-dose treatment in a variety of non-haematological malignancies. Frei, Peters and colleagues at the Dana Farber Cancer Institute led this research using autologous bone marrow to support the patients during recovery from escalating multiple alkylating-agent chemotherapy given to patients with advanced refractory solid cancers. This was based on firm pharmacological principles (vide supra) but the problems of acquired or inherent chemoresistance soon became apparent, as did the problem of acute and often lethal treatment-induced toxicity.[62,64] Amongst the positive outcomes of such approaches, however, the relative responsiveness of breast cancer became apparent.

Eder and colleagues showed that 50% of selected patients with metastatic disease could achieve objective responses, with 25% achieving temporary CRs.[65] Subsequent clinical trials indicated that in metastatic breast cancer high-dose chemotherapy is feasible and produces an objective response in 70%–90% of tumours, with 30%–60% in apparent CR, many converted by the high-dose therapy from induction regimens where the CR rate is around 10%.[49,63–73]

Studies in patients with newly diagnosed metastatic disease or in continuing objective response to induction chemotherapy could achieve CR rates in excess of 50%, with 25% of these CRs durable beyond 5 years.

The reason that the highest response rates are seen in patients who have demonstrated an objective response to the induction chemotherapy is clearly because they have been selected as having chemosensitive tumours. This experience appears to mimic the experience of the haematological malignancies including lymphomas where reduction of the tumour burden by remission induction chemotherapy is emerging as the best strategy.

The toxicity of the earlier experiments was extremely high, with up to 25% immediate or early treatment-associated mortality.[61] However, with improved haemopoietic support morbidity and mortality has been substantially reduced. For some agents such as cyclophosphamide, cytokines alone can provide adequate rescue without the need for bone marrow or stem cell autografts. The latter technique, replacing bone marrow autografting, has not yet been used widely or for long enough to assess the relative benefits and disbenefits in breast cancer treatment as compared to bone marrow autografting; however the early experience in terms of acute outcome looks very promising. Several studies in metastatic breast cancer have demon-

strated the ability of high-dose chemotherapy to increase CR rates converting from partial response achieved in induction therapy. This is important because the achievement of high CR rates could represent a first step towards curative treatment in this setting. The duration of response in high-dose therapy varies between 6 and 20 months and survival rates at 1 and 2 years are between 45% and 65%. These results from non-randomised trials do not indicate prolonged survival for high-dose chemotherapy for all patients, but some are alive and free of disease at 5–10 years, suggestive of a very significant antitumour effect not seen with conventional chemotherapy.[59] The data are summarised in Tables 4–8.

However, the very uncontrolled nature of the studies, with variable selection criteria and the variety of treatments involved, makes it impossible to evaluate the true impact of high-dose chemotherapy outside randomised clinical trials.[74,75] It is difficult to assess whether one regimen is superior to the other and the underexplored area is of patient selection, particularly germane to the metastatic breast cancer population where the natural history of the disease is so extraordinarily variable. This is a subject that deserves far greater attention. Even allowing that most American trials have focused on the treatment of hormone-insensitive disease, nevertheless any experienced clinician is only too aware of the wide range in the natural history of metastatic disease. For some patients survival is measured in weeks from first recurrence, whereas for others survival may extend even beyond a decade of tolerable life with secondary cancer. These variations were sharply illustrated by the data from Guys Hospital in their 1993 report of an audit of some 790 patients managed by chemotherapy for recurrent disease. Similar points emerge from Eddy's sceptical analysis of the outcomes of intensive therapy for advanced disease based on small uncontrolled phase 2 trials.

Developed from clinical and laboratory experience, most of the high-dose regimens are based on intensive alkylating combinations which are very effective theoretically and have been shown to be practically applicable. Theoretically, it is important that alkylating agents should be considered after induction with antimetabolites and anthracyclines because the multidrug resistance phenotype germane to the drugs in the induction regimen is not thought to be relevant to the alkylating agent effect. The most widely used regimen has been the cyclophosphamide, thiotepa, carboplatinum (CTCb) regimen developed at the Dana Farber Cancer Institute.

Table 4. Single-agent high-dose studies in failed or refractory patients (17 studies)

Total pts	Response rate	RDI
74	6 CR; 21 PR	2–10 fold

Table 5. Combination high-dose chemotherapy (34 studies including 6 total body irradiation)

Total pts	Response rate	Response duration	Main regimens
247	17% CR; 69% PR	3–42 mo	C or CT or CL or CP

Abbreviations: see footnote to Table 2.

Table 6. High-dose chemotherapy for metastatic cancer previously untreated

Total	Response rate	Remission duration	Regimens
53	47% CR; 32% PR	13–120+ mo (17%)	CBP*[2]/ CAU/CTP

CBP = Cyclophosphamide, BCNU and cisplatinum; CAU/CTP = cyclophosphamide, adriamycin/cyclophosphamide, thiotepa. * 5 toxic deaths (22%) in one study.

Table 7. Chemointensification for sensitive metastatic breast cancer

Total	Post-induction	After ABMT	Remission duration
306	30% CR; 50% PR	58% CR	1–45 mo (28%)

Table 8. Dose intensification for stage III disease

Total	Response rate	Remission duration
56	50% CR	5–37 mo (54%)

Published by Antmann, in 29 cases of advanced breast cancer an 80% response rate was seen with only one toxic death. The tolerance of high-dose chemotherapy has been improved with better support expertise, use of growth factors and particularly by the supplementation or replacement of ABM transplantation (ABMT) by PBPC transplantation (PBPCT).

Table 9. Ongoing randomised trials in 1995

A. Multiple node positive adjuvant (PBSC supported): aim 300–500 pts each	
CALGB, USA	Induction CAF × 4, then CBP high-dose vs standard
ECOG, USA	Induction CAF × 4, then CT vs observation
Anglo–Celtic	Induction Dox × 4, then C/CT vs CMF × 8
Anglo–French	Induction FEC × 4, then CTCb vs FEC × 2
Scandinavian	Induction chemo, then CTCb vs observation
B. Metastatic disease	
Duke, USA (500+, ongoing)	AFM × 4 CRs CBP vs observation
European (586, commenced)	CAF etc. × 4 responders CTCb vs observation
UK/Irish (planned)	ECF infusional × 6 vs AC/C/M/CT — escalating multiple high-dose

CTCb = Cyclophosphamide, carboplatinum, thiotepa; AFM = adriamycin, 5-FU, methotrexate; ECF = epirubicin, cisplatinum, 5-FU; AC = adriocyclophosphamide; M = melphalan; CT = cyclophosphamide, thiotepa.

Results for late phase II studies have shown that PBPCT following high-dose chemotherapy gives an earlier reconstitution both of neutrophils, and particulary and rather surprisingly of blood platelets, compared with ABMT. The reduced number of platelet transfusions required and the shorter period of hospital stage is now beginning to show economic benefits as well as toxicity benefits for patients.

Finally in view of the very poor results for long-term outcome for stage III inoperable disease,[63] there seems to be a good case for examining intensified treatment; the limited number of studies that have been performed in this area are summarised in Table 9.

Conclusions — future directions

What can we conclude and hope to see in the next few years?

(1) Laboratory studies and imperfect retrospective analyses of conventional chemotherapy have created a climate of active interest within the clinical community in experimenting with dose-intensive chemotherapy.

(2) There seems to be a consensus in favour of combination alkylating agents to maximise anti-cancer and rescuable antimarrow stem cell effects, whilst producing sublethal second-organ toxicity.

(3) PBPCT is replacing ABMT as the routine rescue technique, on grounds of cost and recovery time. The mature results of this changed technology for support have yet to be seen in terms of the risks of late, poor engraftment and the potential benefits in terms of acute complications (faster engraftment) and tumour kill (reduced contamination?).

(4) Whilst experiments continue to examine the impact of tumour contamination of blood harvests or bone marrow harvests, inadequate attention has been paid in metastatic disease to patient selection.

(5) The above emphasises the urgent need to continue experiments; but in the form of randomised clinical trials to prove or disprove the true value of this promising but unproven technique.

(6) Within the conventional dose range, the pragmatic application of schedule alteration for 5-FU has proved promising. Trials in metastatic disease and in primary therapy will need to be completed to assess its relative benefit.

(7) Finally, there seems to be a continuing growth of interest in multiple high-dose therapy regimens using stem cells collected earlier in the therapy to rescue sequential myeloablative treatments. This possibility has been realised because of stem cell technology and is being pursued with enthusiasm and with promising early results in one or two US centres.[62]

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