PERGAMON

European Journal of Cancer 36 (2000) S1–S3

European Journal of Cancer

www.ejconline.com

Introduction

Optimising chemotherapy dose density and dose intensity: new strategies to improve outcomes in adjuvant therapy for breast cancer

A.M. Gianni[a], M.J. Piccart[b,*]

[a]*Department of Medical Oncology, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy*
[b]*Chemotherapy Unit, Department of Internal Medicine, Institut Jules Bordet, Association Hospitalière de Bruxelles, Centre des Tumeurs de l'ULB, Rue Héger-Bordet, B-1000 Brussels, Belgium*

Efficacy is the priority in the administration of adjuvant chemotherapy to patients with breast cancer. However, haematological toxicity is commonly encountered with many cytotoxic regimens and is usually the reason for the clinical practice of reducing the dosage or delaying the administration of the next cycle of chemotherapy [1,2]. Either approach will reduce the dose intensity of treatment. The procedure will achieve some reduction in acute toxicity, but at the expense of a possible loss of therapeutic effect.

Curative treatment of most tumour types is based on the administration of multiple cycles of regularly scheduled chemotherapy. These principles are derived from *in vitro* studies in experimental tumour cell lines, animal xenograft models, and mathematical modelling of the tumour response. The growth of human breast tumours can be modelled by 'Gompertzian' kinetics. In simple terms, this means that the proportion of cells killed is greater when the number of cells present is low, but also that the tumour regrowth is more rapid when cell numbers decrease. Mathematical modelling of tumour cell kill and regrowth based on 'Gompertzian' kinetics and validated by clinical data has been elegantly proposed by Norton to show the effect of varying the dose and intensity of cytoreductive agents [3]. The model can also be viewed as an illustration of the consequences of chemotherapy dose reduction and delay. In the Ridgeway osteosarcoma model in rodents [4], a reduction in dose intensity of cyclophosphamide and melphalan decreased the cure rate without affecting the rate of complete remission. Whilst animals can never model perfectly the human situation, the clinical message from this would be that apparently satisfactory results in the short term following *ad hoc* dosage adjustment may be obscuring a loss of long-term survival for the patient.

Dose intensity is a function of dose and frequency of administration. Hryniuk and colleagues defined dose intensity as the amount of drug delivered per unit of time (mg/m^2/week), and applied it retrospectively to show a clear relationship between dose intensity and outcome in breast cancer patients, from various clinical data using differing doses, schedules and cycles of chemotherapy in both adjuvant and metastatic settings [5,6]. They also proposed the concept of relative dose intensity (RDI), in which the amount of drug administered per unit of time is expressed as the fraction of that used in the standard regimen [7]. More recently, Hryniuk and coworkers have proposed a single scale which they have used to compare dose intensities of different chemotherapy regimens in breast cancer, known as summation dose intensity (SDI). The SDI is made up of unit dose intensities of single agents that produce a specified response rate. When dose-intensity trials of adjuvant chemotherapy or in metastatic disease were analysed, it appeared that positive and negative trials could be distinguished according to whether a particular increment in SDI units had been achieved between the treatment arms [8].

Despite the fact that chemotherapy dose reduction and delay feature routinely in clinical trial protocols, it is only in recent years that relative or received dose intensities (RDIs) have begun to be commonly reported as part of clinical trials. When assessing the effectiveness of a particular protocol, it is clearly important to know the influence of dose reductions and delays by using a variable such as RDI, in order to judge if the trial is a valid comparison of the specified regimens or if suboptimal doses have been administered.

1. The effect of dose intensity on outcome

Dose intensity has been shown to correlate with outcome in prospective clinical studies in various tumour

* Corresponding author. Tel.: +32-2-541-32-06; fax: +32-2-538-08-58.

E-mail address: mpiccart@ulb.ac.be (M.J. Piccart).

PII: S0959-8049(99)00258-0

types, including breast cancer [9–11]. The potential for such a relationship was illustrated by an observation by Bonadonna and colleagues in their follow-up of the study comparing adjuvant cyclophosphamide, methotrexate and 5-fluorouracil (CMF) chemotherapy plus surgery with surgery alone in breast cancer patients [12]. Dose reduction was employed routinely in the case of toxicity or for older patients. Over a 20-year follow-up, patients receiving less than 85% of the intended dose appeared to have a markedly poorer survival. The effect in clinical practice may be more pronounced; it has been estimated that the CMF regimen is used in the community at approximately half the dose intensity originally shown to be effective [2]. Moreover, in a recent review, Goldhirsch and colleagues observed that strategies which result in a lower dose intensity provide inferior results in both the adjuvant setting and in metastatic breast cancer [13].

2. Haematopoietic growth factors (HGFs)

Recombinant HGFs such as granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) have advanced the use of chemotherapy. By increasing neutrophil count recovery and shortening the duration of the nadir neutrophil counts induced by cytotoxic chemotherapy, their use can reduce the incidence and duration of complications such as the infections associated with neutropenia, with potential savings in resource utilisation. The 1994 ASCO practice guidelines on the use of HGFs recommend secondary administration, or secondary prophylaxis, to protect against new episodes of febrile neutropenia or chemotherapy dose modifications in subsequent cycles of treatment in patients who have experienced one of these complications in an earlier course [1]. Primary prophylaxis with CSFs (covering all cycles of chemotherapy) is recommended when the risk of febrile neutropenia is expected to exceed 40% [1].

Support with HGFs has been widely employed to evaluate the effect on outcome of intensified chemotherapy schedules by removing the obstacle of dose-limiting neutropenia [14]. Perhaps most importantly, the reduction in acute toxicity permits administration of the next cycle of chemotherapy at the planned dose and on schedule, with the intention of optimising outcome. Several studies have confirmed the feasibility of this approach, with higher dose intensities being achieved in patients receiving treatment with r-metHuG-CSF [15–17]. A study showing improved disease-free survival with adjuvant chemotherapy supported by r-metHuG-CSF is reported in this supplement by Untch and colleagues [14]. Whilst dose (intensity) was not the only variable, the intensified regimen proved effective and feasible. It is important to remember that the support of dose-intensified chemotherapy is not an approved indication for CSF use, although they are usually included in clinical trials of such strategies. In addition, whilst they are effective in preventing neutropenia and its complications, other unrelated toxicities may in turn become dose limiting.

In many countries, physicians are working in an increasingly cost-constrained environment and additional treatments such as HGFs have to be justified on the grounds of cost-effectiveness. This means that the additional costs of treatment have to be measured in relation to the outcome of therapy. Of course, not every patient will experience the depths of neutropenia that cause infectious complications or chemotherapy dose modification. For example, in Bonadonna's study [12], approximately one-third of patients received reduced doses of CMF chemotherapy because of haematological toxicity.

Early identification of patients at high risk of dose reduction and delay would be an important and rational way to use recombinant G-CSF support to ensure delivery of planned dose on time. There is little prospectively validated information on pretreatment risk factors predictive of postchemotherapy neutropenic complications. However, the utility of risk modelling to identify those patients most likely to benefit from the rational application of recombinant G-CSF to support optimal chemotherapy is presented. It is hoped that this approach to improving delivery of chemotherapy at the planned dose on time will improve overall clinical outcome at a reasonable cost.

Hence, when chemotherapy is given with curative intent, we believe that it is important to avoid reductions and delays in chemotherapy if the best possible outcome is to be achieved. We shall discuss how future advances in adjuvant chemotherapy may achieve these goals, including dose intensification and the development of new chemotherapeutic regimens.

References

1. American Society of Clinical Oncology recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines. *J Clin Oncol* 1994, **12**, 2471–2508.
2. DeVita VT Jr. Principles of cancer management: chemotherapy. In DeVita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology*, 5th edn. Philadelphia, Lippincott-Raven, 1997, 333–347.
3. Norton L. Evolving concepts in the systemic drug therapy of breast cancer. *Semin Oncol* 1997, **24**(Suppl. 10), S10-3–S10-10.
4. Skipper H. Data and analyses having to do with the influence of dose intensity and duration of treatment (single drugs and combinations) on lethal toxicity and therapeutic response of experimental neoplasms. *Southern Research Institute Booklet 13*. Birmingham, Alabama, USA, Southern Research Institute, 24 December 1986. [NB - the reference is the whole booklet.]
5. Hryniuk W, Levine MN. Analysis of dose intensity for adjuvant chemotherapy trials in stage II breast cancer. *J Clin Oncol* 1986, **4**, 1162–1170.

6. Hryniuk W, Bush H. The importance of dose intensity in chemotherapy of metastatic breast cancer. *J Clin Oncol* 1984, **2**, 1281–1287.
7. Hryniuk WM. Average relative dose intensity and the impact on design of clinical trials. *Semin Oncol* 1987, **14**, 65–74.
8. Hryniuk W, Frei E 3rd, Wright FA. A single scale for comparing dose-intensity of all chemotherapy regimens in breast cancer: summation dose-intensity. *J Clin Oncol* 1998, **16**, 3137–3147.
9. Tannock IF, Boyd NF, DeBoer G, *et al*. A randomized trial of two dose levels of cyclophosphamide, methotrexate, and fluorouracil chemotherapy for patients with metastatic breast cancer. *J Clin Oncol* 1988, **6**, 1377–1387.
10. Wood WC, Budman DR, Korzun AH, *et al*. Dose and dose intensity of adjuvant chemotherapy for stage II, node-positive breast carcinoma. *N Engl J Med* 1994, **330**, 1253–1259.
11. Budman DR, Berry DA, Cirrincione CT, *et al*. Dose and dose intensity as determinants of outcome in the adjuvant treatment of breast cancer. *J Natl Cancer Inst* 1998, **90**, 1205–1211.
12. Bonadonna G, Valagussa P, Moliterni A, *et al*. Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer. *N Engl J Med* 1995, **332**, 901–906.
13. Goldhirsch A, Coates AS, Colleoni M, *et al*. Adjuvant chemoendocrine therapy in postmenopausal breast cancer: cyclophosphamide, methotrexate, and fluorouracil dose and schedule may make a difference. *J Clin Oncol* 1998, **16**, 1358–1362.
14. Untch M. Dose-intensification (DI) of anthracycline in the adjuvant treatment of high-risk breast cancer (HRBC) and c-erbB-2 overexpression. *Proc Am Soc Clin Oncol* 1998, **17**, 103a (abstract 395).
15. Pettengell R, Gurney H, Radford JA, *et al*. Granulocyte colony-stimulating factor to prevent dose-limiting neutropenia in non-Hodgkin's lymphoma: a randomized controlled trial. *Blood* 1992, **80**, 1430–1436.
16. Trillet-Lenoir V, Green J, Manegold C, *et al*. Recombinant granulocyte colony stimulating factor reduces the infectious complications of cytotoxic chemotherapy. *Eur J Cancer* 1993, **29A**, 319–324.
17. Therasse P, Mauriac L, Welnicka M. Neo-adjuvant chemotherapy in locally advanced breast cancer (LABC): an EORTC-NCIC-SAKK randomized phase III study comparing FEC (FU, epirubicin, cyclophosphamide) vs high-dose intensity EC + G-CSF (Filgrastim). *Proc Am Soc Clin Oncol* 1998, **17**, 124a (abstract 472).