available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Appropriate chemotherapy, optimal results

A teaching course under the auspices of EORTC 10–11 November 2006, Nice, France

Co Chairs: David Cameron[a], *Matti Aapro*[b,*]

[a]*NCRN Co-ordinating Centre, Cookridge Hospital, Leeds, UK*
[b]*Doyen IMO Clinique de Genolier, Genolier, Switzerland*

1. Introduction

The symposium '*Appropriate Chemotherapy, Optimal Results*' held in Nice in November 2006 provided a valuable update on progress in the treatment of breast cancer and lymphoma, including current views on the treatment of elderly patients. A key focus of this symposium was the importance of delivering effective chemotherapy of sufficient dose intensity to maximise clinical outcomes, and the role of appropriate supportive care in facilitating this by avoiding dose delays and reductions. This supplement provides an overview of these important topics, based upon key presentations at this CME-accredited meeting, which attracted distinguished faculty from both the EU and the USA.

In breast cancer, preoperative neoadjuvant systemic therapy (PST) is now an accepted treatment modality, which has been shown to be associated with equivalent or improved survival rates to adjuvant therapy. In our first paper, Dr Gunter von Minckwitz of the German Breast Group (Neu-Isenberg, Germany) reviews our current knowledge of PST, the principal aims of which are to obtain freedom from disease and to improve surgical options. PST can also provide important early information on tumour biology and responsiveness to chemotherapy. At present, doxorubicin/taxane-based PST regimens show the highest efficacy for breast cancer patients, when trastuzumab is not indicated. However, such regimens are known to be associated with high incidences of haematological toxicity, requiring proactive support with growth factors.

As in other malignancies, an area of increasing interest in breast cancer therapy is the potential to improve outcome by the administration of dose-dense chemotherapy regimens. Our second paper, by Dr Larry Norton of Memorial Sloan-Kettering Cancer Center (New York, USA) provides a concise overview of current experience with dose-dense regimens in the adjuvant breast cancer setting. Results with such regimens are encouraging. In particular, the findings of the large CALGB 9741 study indicate that there is a good case for widespread adoption of this approach. In this study of 2005 women with node-positive primary breast cancer, dose-dense doxorubicin, cyclophosphamide and paclitaxel chemotherapy with granulocyte colony stimulating factor (G-CSF) support significantly improved disease-free survival with a similar trend for overall survival compared to standard therapy.[1] An interim analysis from a Canadian randomised trial (NCIC CTG MA.21) comparing CEF (cyclophosphamide (C), epirubicin (E) and fluorouracil (F) with dose-dense EC/T (E and C followed by paclitaxel [T]) or AC/T (doxorubicin [A]) found non dose-dense AC/T to be inferior to CEF or EC/T in terms of relapse-free survival in high-risk operable breast cancer.[2] However, the authors conclude that it is still too early to detect any difference between CEF and dose-dense EC/T so a dose-dense approach may still add benefit in this setting.

The subsequent paper, by Prof. David Cameron of the National Cancer Research Network (NCRN) (Leeds, UK), addresses the problem of myelotoxicity and its management in breast cancer patients. The incidence of myelotoxicity varies considerably with chemotherapy regimen, with anthracycline-taxane combinations generally producing the most significant myelosuppression. In addition to the costs and inconvenience for patients of hospitalisation, due to the life-threatening nature of febrile neutropenia (FN), myelotoxicity can have a significant impact on the delivery of chemotherapy regimens at optimal relative dose intensity (RDI), thereby compromising treatment efficacy and outcome.[3] A

Sources of support: Amgen (Europe) GmbH provided funding for the preparation of this supplement where indicated.

* *Corresponding author:* Matti Aapro, Doyen IMO Clinique de Genolier, Genolier, Switzerland. Tel: +41 22 366 9106; fax: +41 22 366 9106.

E-mail address: maapro@genolier.net.

1359-6349/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.

practice review found that up to 45% of patients (n = 1111) with early-stage breast cancer receiving adjuvant chemotherapy experienced at least one dose delay or reduction, with 58% of delays and 53% of dose reductions being neutropenia related.[4] In a 30-year follow up of breast cancer patients treated with adjuvant cyclophosphamide, methotrexate, and fluorouracil in three randomised trials, a post-hoc analysis demonstrated that relapse-free survival was 42% among patients who received optimal doses of chemotherapy (≥85% of the planned dose) compared with 26% in those who received <85% of the planned dose.[5] In this regard, the use of G-CSF support can play an important role in the prevention of neutropenia and the maintenance of RDI. The use of antibiotic prophylaxis may not be as efficient as G-CSF for preventing FN and is not widely recommended.

European Organisation for Research and Treatment of Cancer (EORTC) guidelines recommend prophylactic G-CSF administration if the overall FN risk of a particular chemotherapy regimen is ≥20%. For regimens with a 10%–20% FN risk, patient risk factors such as age must be taken into account when considering G-CSF prophylaxis. Available data show that age ≥65 years is consistently associated with an increased FN risk;[6] however, healthy elderly patients with breast cancer can and should receive the same standard adjuvant chemotherapy as younger patients, with appropriate G-CSF support. The EORTC guidelines also recommend that G-CSF support is mandatory with the administration of dose-dense chemotherapy regimens. A meta-analysis of eight randomised controlled trials in patients receiving dose-intensive chemotherapy regimens showed that G-CSF use was associated with a significantly reduced risk of FN (odds ratio 0.38; 95% confidence interval: 0.29–0.49) compared with no G-CSF.[7] The risks of documented infection and infection-related mortality were also reduced with G-CSF administration.

The use of dose-dense chemotherapy regimens is also showing promise in the treatment of lymphoma, as detailed in the paper by Dr Carsten Zwick of the German High-Grade Non-Hodgkin Lymphoma (NHL) Study Group, led by Professor Michael Pfreundschuh. In fact, this approach has become standard in the treatment of aggressive lymphomas in some regions. In this therapy area, the introduction of the CD20-targeted monoclonal antibody, rituximab, and its combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy represents a major advance in the treatment of aggressive lymphomas. The finding of the RICOVER-60 trial[8] that bi-weekly rituximab with CHOP-14, in contrast to 3-weekly application with CHOP-21, improves outcome in patients with poor prognosis as much as in those with a good prognosis suggests that not only dose-dense chemotherapy, but also dose-dense administration of the antibody contribute to the high efficacy of the R-CHOP-14 regimen. Further studies are required to identify the optimal chemotherapy partner for rituximab.

In the final paper of this supplement, Dr Ercole Brusamolino (University of Pavia, Italy) discusses the use of pegfilgrastim support to manage the myelotoxicity associated with the R-CHOP-14 regimen. The FN risk of the basic CHOP-14 regimen is 17–20% when supported with G-CSF.[9] Furthermore, delivery of chemotherapy is optimised, as demonstrated in the NHL-B1 study in NHL patients, where the RDI was 97% for the CHOP-14 regimen with G-CSF support.[10] Similarly, studies in patients with aggressive B-cell NHL[11] and diffuse large B-cell lymphomas[12] showed that with G-CSF support over 90% of R-CHOP-14 cycles could be administered at the planned dose and time.

In summary, the use of dose-dense chemotherapy regimens ***with appropriate supportive care*** and the introduction of new agents such as taxanes and biologicals such as rituximab offer the potential for further improvements in the efficacy of chemotherapy for breast cancer, lymphoma and other malignancies. This supplement provides an exciting overview of the latest thinking in this field and further developments are awaited with interest.

2. Conflict of interest statement

David Cameron has received honoraria from Amgen, Pfizer, Sanofi-Aventis, F. Hoffmann La-Roche and BMS. Matti Aapro has received grants from and serves on an Advisory Board and Speaker's Bureau for Amgen, F. Hoffmann La-Roche and Sanofi-Aventis.

3. Acknowledgement

Gardiner-Caldwell Communications (GCC), Macclesfield, UK assisted in the writing of this manuscript; funding was provided by Amgen (Europe) GmbH.

REFERENCES

1. Hudis C, Citron M, Berry D, et al. Five year follow-up of INT C9741: dose dense (DD) chemotherapy (CRx) is safe and effective. *Presented at the 28th Annual San Antonio Breast Cancer Symposium*, December 8–11, 2005 [abstract 41].
2. Burnell M, Levine M, Chapman JA, et al. A randomised trial of CEF versus dose dense EC followed by paclitaxel versus AC followed by paclitaxel in women with node positive or high risk node negative breast cancer, NCIC CTG MA.21: results of an interim analysis. *Presented at the 29th Annual San Antonio Breast Cancer Symposium*, December 14–17, 2006 [abstract 53].
3. Chirivella I, Bermejo B, Insa A, et al. Impact of chemotherapy dose-related factors on survival in breast cancer patients treated with adjuvant anthracycline-based chemotherapy. *J Clin Oncol* 2006;24:44s [abstract 668].
4. Link BK, Budd GT, Scott S, et al. Delivering adjuvant chemotherapy to women with early-stage breast carcinoma: current patterns of care. *Cancer* 2001;**92**:1354–1367.
5. Bonadonna G, Moliterni A, Zambetti M, et al. 30 years' follow up of randomised studies of adjuvant CMF in operable breast cancer: cohort study. *BMJ* 2005;**330**:217.
6. Aapro MS, Cameron DA, Pettengell R, et al. EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphomas and solid tumours. *Eur J Cancer* 2006;**42**:2433–2453.
7. Lyman GH, Kuderer NM, Djulbegovic B. Prophylactic granulocyte colony-stimulating factor in patients receiving dose-intensive cancer chemotherapy: a meta-analysis. *Am J Med* 2002;**112**:406–411.

8. Schubert J, Reiser M, Wenger M, et al. Bi-weekly dosing preserves the efficacy of rituximab in elderly patients with poor-prognosis DLBCL: results from the RICOVER-60 trial of the German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL). *J Clin Oncol* 2006;24:430s.
9. Gregory SA, Case DC Jr, Bosserman L, et al. Fourteen-day CHOP supported with granulocyte colony-stimulating factor in patients with aggressive non-Hodgkin's lymphoma: results of a phase II study. *Clin Lymphoma* 2003;**4**:93–98.
10. Pfreundschuh M, Trümper L, Kloess M, et al. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of young patients with good-prognosis (normal LDH) aggressive lymphomas: results of the NHL-B1 trial of the DSHNHL. *Blood* 2004;**104**:626–633.
11. Lopez A, Fernandez de Sevilla A, Castaigne S, et al. Pegfilgrastim supports delivery of CHOP-R chemotherapy administered every 14 days: a randomized phase II study. *Blood* 2004;**104** [abstract 3311].
12. Brusamolino E, Rusconi C, Montalbetti L, et al. Dose-dense R-CHOP-14 supported by pegfilgrastim in patients with diffuse large B-cell lymphoma: a phase II study of feasibility and toxicity. *Haematologica* 2006;**91**:496–502.