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Critical Reviews in Oncology/Hematology 66 (2008) 171–180

CRITICAL REVIEWS IN
Oncology
Hematology
Incorporating Geriatric Oncology

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Weekly docetaxel versus CMF as adjuvant chemotherapy for elderly breast cancer patients: Safety data from the multicentre phase 3 randomised ELDA trial☆

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Accepted 31 October 2007

Contents

Abstract

Within an ongoing multicentre phase 3 randomised trial (ELDA, cancertrials.gov ID: NCT00331097), early breast cancer patients, 65–79 years old, with average to high risk of recurrence, are randomly assigned to receive CMF (cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2, fluorouracil 600 mg/m^2, days 1–8) or docetaxel (35 mg/m^2 days 1–8–15), every 4 weeks. Here we report an unplanned safety

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1040-8428/$ – see front matter
doi:10.1016/j.critrevonc.2007.10.006

analysis prompted by an amendment introducing creatinine clearance as a tool to adjust methotrexate dose. Before such change, 101 patients with a median age of 70 were randomly assigned CMF (53 patients) or docetaxel (48 patients). At least one grades 3–4 toxic event of any type was reported in 40 (75.5%) and 19 (39.6%) patients with CMF and docetaxel, respectively ($p = 0.0002$). Grades 3–4 hematological events were observed in 37 (69.8%) vs. 4 (8.3%) cases ($p < 0.0001$) and grades 3–4 non-hematological toxicity in 12 (22.6%) vs. 15 (31.2%) patients ($p = 0.11$), with CMF and docetaxel, respectively. A higher incidence of anemia, neutropenia, thrombocytopenia and febrile neutropenia was reported with CMF. Constipation, mucositis, nausea and vomiting were more common with CMF; diarrhoea, abdominal pain, dysgeusia, neuropathy and liver toxicity were more frequent with docetaxel. No significant interaction was found between the occurrence of severe toxicity and baseline variables, including creatinine clearance and geriatric activity scales. In conclusion, weekly docetaxel appears to be less toxic than CMF in terms of hematological toxicity.

Keywords: Breast cancer; Elderly; Adjuvant; Docetaxel; Phase 3; CMF

1. Introduction

Breast cancer is the first cause of cancer death among women older than 65 years and its incidence increases with advancing age [1]. The Early Breast Cancer Trialist' Collaborative Group (EBCTCG) meta-analysis suggested that elderly breast cancer patients may benefit from adjuvant chemotherapy, but to a smaller extent than younger women [2]. However, elderly patients are not adequately represented in clinical trials of adjuvant chemotherapy and there are few ongoing studies of adjuvant chemotherapy specifically planned for elderly breast cancer patients [3–5]. Therefore, therapeutic choice for elderly patients is currently not based on reliable scientific evidence.

The combination of cyclophosphamide, methotrexate and fluorouracil (CMF) is the most frequently used adjuvant treatment regimen for elderly breast cancer patients, but reasonable concern exists on its use in this population [6]. Crivellari et al. examined the toxicity encountered in elderly (≥65 years old) node-positive breast cancer patients compared with younger (<65 years) postmenopausal patients, within the International Breast Cancer Study Group (IBCSG) trial VII, in which postmenopausal patients, prevalently with estrogen-receptor positive tumors, were randomised to tamoxifen or tamoxifen plus three cycles of CMF. This study showed that CMF tolerability and effectiveness were both reduced in older patients as compared with younger women [7]. In a subsequent retrospective analysis on the compliance and safety of adjuvant CMF in patients older than 60 years treated as clinical practice, we found that the feasibility of six cycles of adjuvant CMF was not different between patients 65 or more years old and patients aged 60–65 years, but with a relevant burden of toxicity [8].

On the basis of these findings, great interest exists in evaluating the role of new effective regimens or drugs, with favourable safety profile in elderly patients. Docetaxel, introduced into clinical practice in the early 1990s, is among most active drugs in breast cancer [9]. It is also effective in the adjuvant setting [10–12]. However, the standard 3-weekly schedule produces relevant side effects, particularly febrile neutropenia, causing concerns regarding its use for elderly patients [13]. The toxicity of docetaxel can be markedly decreased when the drug is administered with a weekly schedule [14,15], that has shown promising activity and excellent tolerability also in elderly advanced breast cancer patients [16].

We are performing a multicentre phase three randomised trial (elderly breast cancer–docetaxel adjuvant study, ELDA; clinicaltrials.gov ID: NCT00331097) to compare weekly docetaxel with CMF as adjuvant treatment of elderly patients with early breast cancer. As of December 2006, CMF schedule has been modified including creatinine clearance for dosing of methotrexate [17]; at that time, a compliance and safety analysis of data collected before the amendment has been decided and is reported hereby.

2. Patients and methods

2.1. Study design

The ELDA study is a phase 3, randomised, multicentre, unblinded trial designed to demonstrate the superiority of weekly docetaxel over CMF as adjuvant treatment in terms of disease-free survival of elderly breast cancer patients. Overall, 178 events and 300 enrolled patients have been planned for the final analysis. The trial is managed by the Clinical Trials Unit of the National Cancer Institute of Naples, that is the sponsor of the study. Patients are randomised centrally by a minimization procedure considering centre, pT and pN category, planned number of chemotherapy cycles and age category as strata. In October 2006, a revision of the Italian Society of Medical Oncology guidelines made available few months before prompted a protocol amendment to adapt the dose of methotrexate according to the Gelman and Taylor formula [17] when creatinine clearance is equal to 60 ml/min or lower, assuming that impaired renal excretion of this drug might affect toxicity in the elderly. Considering that the collection of safety data for comparing standard CMF (not adjusted by creatinine clearance) versus weekly docetaxel would have been definitively completed soon after the implementation of the amendment, we proposed and Independent Ethical Committees approved that an unplanned compliance and safety comparison between weekly docetaxel and standard CMF could be done and reported. Sample size for this