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ORIGINAL ARTICLE

T. Palangié · J.Y. Pierga · P. Pouillart

Dose-intense salvage therapy after neoadjuvant chemotherapy: feasibility and preliminary results

Abstract Breast cancer patients who, following treatment with primary chemotherapy (FAC 50) present an axillary node involvement of more than 4 nodes together with clinically palpable residual disease (minor response to chemotherapy) and the presence of tumour cell emboli in lymphatics have a very poor outcome. DFS rates of 50 patients treated between 1990 and 1994 were 31% at 5 years. Our aim was therefore to evaluate an entirely different therapeutic regime in these very high risk patients. 32 patients selected for these criteria entered a pilot study consisting in treatment with 3 four weekly cycles of vinorelbine, ifosfamide, cisplatinum followed by a high dose chemotherapy (HDCT) course and rescue by peripheral hematopoietic stem cells which had been collected by cytapheresis after the second course of chemotherapy. HDCT consisted of thiotepa, L-Pam, CBDCA (800 mg/m^2 d1), ifosfamide and mesna. Following primary chemotherapy, 14 patients had breast conservation and 18 had a modified mastectomy. Median number of involved lymph nodes was 11 (range 4–26). 29 patients received the complete HDCT course. Median age was 40 (range 24–59). Engraftment was prompt with a median of 10 days to leucocyte recovery to 1000/μl and 9 days to platelet recovery. One patient developed reversible renal failure, and subsequently died of Gram–septicemia. To date, with a median follow up of 20 months (range 14–36), 6 patients have relapsed and 2 patients have died. It is too early to make any firm conclusions, but we feel that this alternative regime is feasible and may prove superior to the classical optimal dose anthracycline-containing regimes in patients who have a tendency to rapidly develop resistance to anthracyclines.

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T. Palangié · J.Y. Pierga · P. Pouillart (✉)
Institut Curie, 26, rue d'Ulm,
F-75005 Paris, France
Tel.: +33-1-442911101

Introduction

In operable breast cancer, neoadjuvant chemotherapy reduces tumour burden and allows more conservative surgery. Despite a reduction in the number of positive nodes, the long-term results (disease-free survival and overall survival) appear to be not significantly different from those following adjuvant chemotherapy. The NSABP B-18 trial compared 4 preoperative courses of AC (doxorubicin, cyclophosphamide) with 4 postoperative courses of the same protocol [1]. In the patients treated by first-line chemotherapy, the pathological nodal status was a major prognostic factor and was not related to clinical response [2]. The two main strategies in the treatment of these patients concern: (1) the systematic axillary dissection in patients with clinical complete response after primary chemotherapy and (2) the efficiency of a second-line of adjuvant chemotherapy whatever the pathological nodal status.

Several previous trials have attempted to improve the outcome of patients who did not respond to primary chemotherapy by either prolonging the treatment course or by treating with "non-cross resistant" secondary adjuvant protocols.

The aim of the present trial was to define the feasibility of dose intensification with autologous stem cell rescue in patients who had a poor response to neoadjuvant chemotherapy.

Patients and methods

Thirty-two high-risk patients with minor or no response after four 3-weekly courses of ACF (Doxorubicin 50 mg/m^2 day 1, cyclophosphamide 500 mg/m^2 days 1 and 8, 5-fluorouracil 500 mg/m^2 days 1 and 8) entered this pilot study.

The dose-intense chemotherapy protocol included two parts. In part 1, the patients received 3 monthly courses of NaPIM combining vinorelbine (20 mg/m^2 days 1 and 8), cisplatin (50 mg/m^2 days 2 and 3), ifosfamide (1.8 g/m^2 days 1, 2, 3) + mesna (2000 mg/m^2 d1 – 4). Peripheral stem cells were collected after the first or second course of chemotherapy. In the second part,

chemotherapy was intensified combining thiotepa (120 mg/m^2 × 4), ifosfamide (2.4 g/m^2 × 4) + mesna (2000 mg/m^2 d1 – 4), melphalan (100 mg/m^2) and carboplatin (CBDCA 800 mg/m^2). Owing to a severe platelet toxicity, the CBDCA was discontinued from this protocol after the first 15 patients had completed their treatment.

Results and discussion

The median age of the patients was 40 years (range 24–59), and 28 of the patients out of 32 were premenopausal. Fifty-two per cent of the tumours had a positive oestrogen receptor status, and the median S-phase fraction determined by flow cytometry was 5.2% (range 0.5–18). Following primary chemotherapy, 14 patients could be treated by breast conservation, 18 had a modified mastectomy. All these patients presented a pathological nodal involvement (median number of positive nodes 11, range 4–28). Eight patients had 4–7 positive nodes, 12 patients had 8–10, and 12 patients had more than 10 positive nodes.

The tolerance of the NaPIM protocol was acceptable with a grade IV leucopenia reported in 28 and hospitalization for febrile neutropenia in 4 patients.

Thirty-two patients were intensified, 15 in the first group with CBDCA and 17 in the second without CBDCA. Engraftment was prompt, with a median of 10 days for leucocyte recovery to 1000/μl and 12 days for platelet recovery to 20 000/μl (21 days for platelet recovery to 50 000/μl). Mucositis grades III and IV was observed in 62% of the patients and fever for more than 7 days in 36%. Two patients of the first group of intensification (with CBDCA) presented lethal complications combining severe thrombocytopenia (< 10 000), renal failure, grade IV mucositis and gram-negative septicemia. The first patient died of a cerebral hemorrhage and the second, after complete recovery, subsequently died of pneumonitis in an intensive care unit. To date, with a median follow up of 25 months (range 19–41), 23 patients are alive in apparently complete remission, 7 patients are alive with recurrent disease, and 2 patients have died.

It is too early to draw any definitive conclusions from this ongoing study. However, this alternative treatment in poorly responding patients after primary chemotherapy is feasible and may prove superior to the classic optimal dose anthracycline-containing regimens in patients who rapidly develop resistance to anthracyclines.

References

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