

Once-per-cycle pegfilgrastim in breast cancer patients treated with docetaxel/epidoxorubicin/cyclophosphamide

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The incidence of neutropenia following combination chemotherapy is significant in breast cancer and impairs patients' quality of life. Colony-stimulating factors significantly decrease the risk of febrile neutropenia (FN). Aim of the present study was to assess the efficacy and safety profile of once-per-cycle pegfilgrastim in reducing FN in breast cancer patients treated with docetaxel (75 mg/m²), epidoxorubicin (75 mg/m²), cyclophosphamide (500 mg/m²) administered every 3 weeks. Thirty-five breast cancer patients were enrolled. Chemotherapy was administered in adjuvant, neoadjuvant and metastatic setting respectively in 26, 4 and 5 patients. Toxicity was monitored with programmed clinical evaluation and blood sampling. All patients completed the therapeutic programme consisting of six cycles for overall 210 cycles. The FN appeared in 6 out of 35 patients (17%), requiring dose reduction in 3 patients. Hypertransaminasemia was registered in two patients. In one patient pegfilgrastim administration was stopped because of skin hypersensitivity reaction. In conclusion, pegfilgrastim was able to maintain doses and timing of docetaxel/epidoxorubicin/cyclophosphamide in almost all breast cancer patients treated in this series. The reduced need for daily administration of colony-stimulating factors, blood sampling, antibiotic therapy and hospitalization has a significant impact in terms of both quality of life and pharmaco-economic evaluations.

Keywords: chemotherapy, breast cancer, symptoms, supportive care, polyethylene glycol-colony-stimulating factors, palliative care.

INTRODUCTION

Taxanes are widely used in breast cancer. Response rates reported with docetaxel are 61% when used as first-line chemotherapy (Chan *et al.* 1999) and 43% as second line (Fumoleau *et al.* 1996) in metastatic breast cancer. Following use as single agents, taxanes were rapidly included in combination chemotherapeutic schemes. In NSABP BP-58 study docetaxel in combination with doxorubicin

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and cyclophosphamide (TAC) achieved a response rate of 72.5% and 35.6 months as median survival in patients with IIIB/IV stage breast cancer (Smith *et al.* 2002). However, febrile neutropenia (FN) was as high as 38%, leading to the recommendation of ciprofloxacin use and growth factors in secondary prophylaxis. In adjuvant setting TAC was compared with 5-fluorouracil/doxorubicin/cyclophosphamide (FAC) reporting significant improvement in disease-free and overall survival (Martin *et al.* 2005). Once again, however, this benefit corresponds to an increased rate of grades 3–4 neutropenia and increased FN in the group of patients treated with TAC (65.5% and 24.7%) as compared with those treated with FAC (49.3% and 2.5%). Therefore, one of the most active chemotherapy regimens used in breast cancer can be poorly tolerated due to serious myelotoxic potential (Martin *et al.* 2006).

The upfront use of colony-stimulating factors (CSFs) in primary prophylaxis significantly reduced FN and other haematologic and not-haematologic side effects. Even quality of life, which resulted worse in patients treated with TAC as compared with those treated with FAC, improved with CSFs used as secondary prophylaxis. American Society of Clinical Oncology (ASCO) guidelines recommend primary prophylaxis with a CSF in the first and subsequent chemotherapy cycles for patients receiving chemotherapy regimens with a high risk (20% or greater) of FN (Smith *et al.* 2006). General consensus is reached on this matter as European Organization for Research and Treatment of Cancer (Kearney *et al.* 2006) and National Comprehensive Cancer Network (Lyman 2005) guidelines on the use of myeloid growth factors are on line with this recommendation. Moreover, primary prophylaxis is recommended when neutropenia could result in chemotherapy dose delays or reductions. The occurrence of FN may be a life-threatening event, often requiring hospitalization and treatment with intravenous antibiotics. Moreover, chemotherapy delays and dose reductions are generally required at the following cycles. There is consistent evidence supporting use of chemotherapy at full and planned doses when administered at curative intent. In patients with breast cancer, results from 30 years of follow-up showed improved relapse-free survival and overall survival benefit for patients receiving at least 85% of the planned chemotherapy dose, compared with patients given lower doses (Bonadonna *et al.* 2005). Summarizing, FN substantially impacts on chemotherapy outcomes, patient quality of life and costs of treatments administered. Granulocyte-CSFs (G-CSFs) are widely used in cancer care in order to overcome the FN induced by chemotherapy and attempts have been made to adminis-

ter G-CSF in a prophylactic way in order to prevent FN in heavily treated patients. A recent overview concluded that prophylactic G-CSF reduces the risk of FN and early deaths, including infection-related mortality even if insufficient data are available to assess the impact of G-CSF on disease-free and overall survival (Kuderer *et al.* 2007). However, multiple administrations of G-CSF are required due to the short half-life of this moiety. In this view, pegylation, the technology of polyethylene glycol (PEG) conjugation, holds significant promise in maintaining effective plasma concentrations of systemically administered drugs that might otherwise be hampered *in vivo* by a number of factors, such as rapid elimination by the kidneys. Pegfilgrastim is a pegylated version of the G-CSF filgrastim that is administered for management of chemotherapy-induced neutropenia. Its dosing schedule has longer intervals between administrations with consequent improved compliance and quality of life in patients with chronic disease (Molineux 2003). On this basis, we performed the present study using primary prophylaxis with once-per-cycle pegylated CSF, pegfilgrastim, administration in breast cancer patients treated with docetaxel/epidoxorubicin/cyclophosphamide (TEC). Aims of the present study were the evaluation of efficacy and safety of pegfilgrastim in primary prophylaxis in breast cancer patients treated with TEC.

PATIENTS AND METHODS

From May 2005 to August 2007, 35 patients (age: 27–68 years, median age: 47.3 years) were enrolled. Pathologic characteristics of primitive tumors are summarized in Table 1. All patients had PS 0 by ECOG. Normal haematologic, hepatic, renal and cardiac functions were required at study entry. The protocol was submitted to independent ethical committees and the approvals had to be obtained prior the study start. Written informed consent was obtained from each participating patient at the entry into the study.

Four patients were treated with neo-adjuvant intent, while 26 patients received chemotherapy after surgery. Five patients showed metastatic involvement by breast cancer: bone in two patients; lung in one patient; pleural effusion, skin and axillary node relapse in one patient; brain and liver in another patient. Two patients were diagnosed with synchronous breast cancer and bone metastases. One patient had bilateral breast cancer and lung metastases. The patients received chemotherapy according to the following schedule: docetaxel 75 mg/m², epidoxorubicin 75 mg/m², cyclophosphamide 500 mg/m². Overall six cycles administered every 21 days were sched-

Table 1. Pathologic characteristics of primitive tumours

Stage	Number of patients
T	
T1	4
T2	24
T3	—
T4	7
N	
N0	2
N1	15
N2	17
N3	1
Grading	
G1	2
G2	13
G3	20
Immunohistochemical profile	
positive/negative ER	21/14
positive/negative PgR	20/15
positive/negative Ki 67	32/3
positive/negative c-erb-B2	8/27

uled. The day after chemotherapy, the patients received 6- μ g pegfilgrastim injection subcutaneously. Blood samplings were performed 10 days after chemotherapy and according to clinical evaluation. The FN was defined as body temperature $\geq 38.2^{\circ}\text{C}$ and neutrophil count $< 0.5 \times 10^3/\mu\text{L}$ on the same day of the fever or the day after. All data concerning adverse events and changes in laboratory changes were collected. Toxicity was evaluated using the National Cancer Institute (NCI) criteria (version 2.0).

RESULTS

All patients completed the therapeutic programme for overall 210 courses of TEC and pegfilgrastim administration. Grade 4 FN was found in 6 out of 35 patients (17%). In all cases FN appeared after the third cycle. The mean duration of neutropenia was 3 days (2–17 days). The FN was treated with intravenous and oral antibiotics only in one patient who presented prolonged FN (17 days) with concomitant grade 2 anaemia (NCI criteria) and grade 3 piastrinopenia (NCI criteria). This patient presented brain and liver metastases. In the other patients only oral antibiotics were used. Full recovery realized within the time of scheduled administration of chemotherapy. In two out of six patients 30% dose reduction was performed after the third cycle; however, grade 3 neutropenia and FN presented again in these two patients, requiring oral antibiotics support.

Pegfilgrastim administration was precautionally stopped in a 29-year-old patient who showed after the fourth cycle of chemotherapy and pegfilgrastim a skin

itchy reaction with erythema and papules spread over the body. Such skin reaction disappeared after antihistamine treatment. After the fifth cycle, the patient was admitted in hospital because of grade 4 neutropenia, grade 2 anaemia and grade 1 piastrinopenia (according to NCI toxicity criteria). Neutropenia recovered with conventional CSFs and intravenous antibiotics.

Pegfilgrastim was generally well tolerated apart from mild bone pain in five patients (14%), requiring sporadic anti-inflammatory drugs. The adverse events reported were typical of chemotherapy administered (i.e. alopecia, nausea, vomiting, fatigue). We also recorded grade 2 hypertransaminasemia appearing following the fourth cycle requiring supportive care and chemotherapy delays in two patients.

DISCUSSION AND CONCLUSIONS

Pegfilgrastim was well tolerated in all patients enrolled in the present study and allowed administration of full doses of chemotherapy without the requirement of delays in almost all patients.

The CSFs represent a significant advancement in supportive care of cancer patients and produce quality of life improvement through the reduction of infections and related hospitalization. Moreover, dose intensity of chemotherapy was increasingly preserved with CSFs. However, haematological recovery requires several injections of filgrastim because of its short half-life. Pegfilgrastim (Neulasta; Amgen, Thousand Oaks, CA) represents an evolution of filgrastim. In fact, pegfilgrastim is a long-acting filgrastim obtained through covalent bound of a 20Kd molecule of PEG to the amino-terminal of filgrastim. This modification implies reduced renal and predominant neutrophil-mediated clearance. Pegfilgrastim half-life and filgrastim half-life are respectively 42 and 3.5–3.8 h. Pegfilgrastim action is lastly self-controlled, because biologic effect is prolonged when neutrophil count is low.

Results of two randomized studies in patients with breast cancer showed that a single dose of pegfilgrastim produces the same effect on neutrophils as 11 injections of filgrastim (Crawford 2003; Molineux 2004). Moreover, pegfilgrastim was as effective as filgrastim in reducing neutropenia in patients with lymphoma treated with chemotherapy (Vose *et al.* 2003). Studies performed until now showed that a single injection of pegfilgrastim has efficacy and safety profile similar to multiple injections of filgrastim (Holmes *et al.* 2002; Siena *et al.* 2003).

Active chemotherapy regimens such as TAC and TEC are increasingly used with significant risk of haematological toxicity. A high incidence of first-cycle FN was

showed in breast cancer patients treated with docetaxel supporting the need to start pegfilgrastim from the first cycle (Vogel *et al.* 2005). A recent cost-minimization analysis has shown that first-cycle use of pegfilgrastim may be cost-neutral in patients in whom the predicted risk of FN is less than 20% (Rader *et al.* 2006). The FN reported in breast cancer treated with TAC ranged from 24.7% to 38% (Nabholtz *et al.* 2001; Smith *et al.* 2002; Martin *et al.* 2005), values higher than 20% which 2006 ASCO guidelines consider as cut-off to justify primary prophylactic CSF use. Very recently, use of CSFs and especially pegfilgrastim found new confirmation from observational studies, which suggest real effectiveness in clinical practice (Morrison *et al.* 2007; Ozer *et al.* 2007).

In our study grade 4 FN was found in 6 out of 35 patients (17%). In all cases FN appeared after the third cycle and the mean duration of neutropenia was 3 days (2–17 days). The FN was treated with intravenous and oral antibiotics only in one patient who presented prolonged FN. These data are similar to those reported in previous studies where comparable even if larger populations were enrolled and treated with prophylactic non-pegylated G-CSF. In fact, the most recent study by Martin *et al.* (2006) enrolled 414 breast cancer patients in adjuvant setting with 50 years median age (range 24–74 years) and 80–100 PS Karnofsky at baseline. They recorded FN in 7.5% of patients treated with TAC schedule and prophylactic administration of G-CSF (filgrastim or lenograstim). Interestingly, 6.5% of patients had grade 4 FN requiring antibiotics and/or hospitalization while in our report only 1/35 (2.8%) patients required intensive treatments.

A single dose of pegfilgrastim plus ciprofloxacin resulted more effective as primary prophylaxis compared with nine filgrastim injections in GEPARTRIO study evaluating neo-adjuvant TAC in breast cancer patients (Von Minckwitz *et al.* 2005).

In this regard, primary aim of practicing oncologists is not only to offer the best chances of care, but also to reduce potential side effects related to chemotherapy and adopt all remedies to preserve patients' quality of life. In this perspective pegfilgrastim represents a powerful tool.

The biotechnology can help clinical practice in oncology, increasing the half-life of well-established drugs through the conjugation with PEG. The latter is useful in order to maintain high plasmatic levels of the drug avoiding repetitive administrations that impair the quality of life of patients affected by a chronic disease such as cancer.

In conclusion, the reduced risk of FN produced by a single injection per cycle of pegfilgrastim induces a consistent improvement in cancer treatment. Moreover,

these findings disclose a new scenario in which biotechnological modifications of biological agents could be useful not only to increase their activity but also to ameliorate the compliance of the patients.

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