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Original Paper

An Open-label, Multicentre, Randomised Phase 2 Study of Recombinant Human Granulocyte Colony-stimulating Factor (Filgrastim) as an Adjunct to Combination Chemotherapy in Paediatric Patients with Metastatic Neuroblastoma

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Administration of combination chemotherapy to children with metastatic neuroblastoma induces profound myelosuppression resulting in chemotherapy treatment delays and febrile neutropenic episodes. The objective of this randomised multicentre study was to assess the incidence, duration and severity of neutropenia when filgrastim is added to induction chemotherapy administered to patients with metastatic neuroblastoma. In this study, 59 patients with metastatic neuroblastoma were randomised to receive chemotherapy (control group, $n = 28$) or chemotherapy plus filgrastim (filgrastim group, $n = 31$). Chemotherapy consisted of four cycles of cyclophosphamide, vincristine and doxorubicin (CADO) alternating at 21-day intervals with cisplatin and etoposide (CDDP–VP16). Filgrastim was administered subcutaneously at a dose of 5 μg/kg/day from day 7 for up to 14 days. The incidence of neutropenia (absolute neutrophil count [ANC] $< 0.5 \times 10^9$/l) in the filgrastim group was not reduced after the first CADO course. However, significant reductions were observed after courses 2, 3 and 4. The duration of neutropenia and of intravenous antibiotic use were significantly reduced in the filgrastim group over the whole study period (9 days versus 26 days, $P < 0.001$; 12 days versus 20 days, $P = 0.04$, respectively). However, the duration of hospitalisation and the incidence of febrile neutropenia were not significantly reduced. Compliance to treatment was good and the ability to administer chemotherapy without treatment delays was significantly better in the filgrastim group ($P < 0.05$). Event-free survival was greater in the filgrastim than in the control group (2.4 years versus 1.3 years; $P = 0.072$). Filgrastim is a beneficial adjunct to combination induction chemotherapy used in the treatment of metastatic neuroblastoma. © **1998 Elsevier Science Ltd. All rights reserved.**

Key words: neuroblastoma, filgrastim, neutropenia, infection, chemotherapy, dose intensity, children
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INTRODUCTION

THE TREATMENT of metastatic neuroblastoma in patients older than 1 year of age is still one of the major therapeutic challenges in paediatric oncology [1]. Despite the use of multimodal induction chemotherapy regimens, less than 70% of patients achieve a complete or very good partial response [2–4]. With the use of intensive regimens, the main dose-limiting toxicity is neutropenia which often results in infections and their related morbidity. Infectious complications of chemotherapy treatment, as well as thrombocytopenia, severely affect the quality of life of those patients whose long-term prognosis is still poor, despite the use of intensive consolidation therapy [5]. Furthermore, prolonged haematological toxicity may be responsible for delays in the administration of

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chemotherapy, resulting in a reduction in dose intensity. This may, theoretically, be subsequently reflected in a reduction in response rates to therapy.

Recombinant human granulocyte colony stimulating factor (r-metHuG-CSF, filgrastim) is a genetically engineered growth factor that stimulates the production and maturation of neutrophils *in vivo*. As an adjunct to antineoplastic chemotherapy regimens in adult patients, filgrastim can reduce the incidence and duration of febrile neutropenia and delays in the administration of chemotherapy [6–8]. While the clinical benefits of filgrastim administration after chemotherapy in accelerating neutrophil recovery are proven in the adult population, the clinical benefits of cytokines after chemotherapy in paediatric patients are still unknown.

Here we report the first randomised study of filgrastim use in children receiving combination chemotherapy for a newly diagnosed paediatric solid tumour. The study was an open-label, randomised, comparative, parallel-group study designed to determine if the administration of filgrastim could reduce the incidence and duration of neutropenia (absolute neutrophil count [ANC] $< 0.5\times10^9$/l) and its clinical sequelae. The clinical endpoints assessed throughout the study were the incidence of febrile neutropenia, the duration of fever, the use of intravenous (i.v.) antibiotics, the incidence of documented infections, the duration of hospitalisation, and the incidence of treatment delays. In addition, the safety of filgrastim administration was monitored.

PATIENTS AND METHODS

Patient population

The protocol was approved by the appropriate institutional review board and all legal guardians of the patients gave informed, written consent. Patients with previously untreated metastatic neuroblastoma as established using the INSS criteria [9] and with evaluable disease (primary site measured by computerised tomography (CT) scan or ultrasonography; metastasis evaluated by ^{123}I-meta-iodo-benzyl-guanidine [MIBG] scan, and bone marrow aspirates and biopsies) were enrolled if they met eligibility requirements. Inclusion criteria were ECOG performance status of 0, 1 or 2; age ≥ 1 year and ≤ 16 years; body weight ≥ 10 kg; apyrexia, unless fever could be attributed to the presence of metastatic disease; no antibiotic therapy before treatment; normal creatinine and liver function tests; ANC $\geq 1\times10^9$/l and platelets $\geq 50\times10^9$/l; and normal cardiac function.

Treatment design and data collection

Chemotherapy patients were enrolled in six centres of the Société Française d'Oncologie Pédiatrique (SFOP). Randomisation was stratified by centre. After verification of eligibility criteria, patients were randomised to receive four alternating courses of chemotherapy on a 21-day schedule [10], with or without filgrastim administered between day 7 and day 20 of each course. Courses 1 and 3 consisted of cyclophosphamide 300 mg/m^2 from day 1 to day 5 (administered i.v., intramuscularly [i.m.] or orally [p.o.]); vincristine 1.5 mg/m^2 i.v. day 1 and day 5; and doxorubicin 60 mg/m^2 i.v. over 3 h on day 5 (CADO). Courses 2 and 4 consisted of etoposide 100 mg/m^2 i.v. over 1 h and cisplatin 40 mg/m^2 i.v. over 24 h on day 1 to day 5 (VP16–CDDP). On day 7 of each course (48 h after the injection of doxorubicin for courses 1 and 3 and 24 h after the end of cisplatin infusion for courses 2 and 4), patients randomised to the treatment group received filgrastim (5 μg/kg/day) once daily by subcutaneous (s.c.) injection for a maximum of 14 days. Filgrastim was discontinued if ANC $\geq 40\times10^9$/l before day 14 of the cycle or ANC $\geq 10\times10^9$/l for more than 2 days after day 14 of the chemotherapy cycle.

Courses of chemotherapy were repeated every 3 weeks providing ANC and platelets counts were $\geq 1\times10^9$/l and 100×10^9/l, respectively; otherwise chemotherapy was delayed until these conditions were met. If a severe infectious episode associated with neutropenia occurred, the doses of chemotherapeutic agents could be reduced by 33% (except for vincristine). If this occurred in courses 1 or 2, this dosage reduction was applied for the next identical chemotherapy cycle.

Laboratory and physical measurements

Records of axillary temperature and drug administration were kept daily. Complete blood counts were taken three times a week. Physical examination, vital signs, weight and ECOG performance status were recorded at least weekly. Renal and liver functions were checked before the initiation of each course. Patients who developed febrile neutropenia (ANC $< 0.5\times10^9$/l with axillary temperature $> 38.0^\circ$C) were hospitalised. Investigations of bacteriological infection were performed and empirical parenteral antibiotic therapy was immediately initiated. During hospitalisation for febrile neutropenia, a full blood count was performed daily. If empirical antibiotic therapy had been instituted for fever of unknown origin, it was discontinued when ANC was $> 0.5\times10^9$/l and the patient had remained afebrile for 24 h (even if the patient was receiving rG-CSF). Duration of antibiotic therapy for bacteriological documented infection was based upon available bacteriological data. All concomitant medications and blood products used were recorded.

Tumour response

Neuroblastoma tumour response was assessed after courses 2 and 4 by using primary tumour measurement and evaluation of metastatic sites with the same methods as for the initial staging procedure. Patients who showed disease progression at any time were removed from study. At the end of the four courses of chemotherapy, patients who had completed the study were treated according to ongoing post-induction treatment protocols of the SFOP [10]. All patients were subsequently followed for relapse, progression and survival outcome until August 1997.

Statistical considerations analysis

Adverse events were recorded at least weekly. The planned sample size was 28 evaluable patients per group, providing 80% power to detect a significant difference at the 5% level based on a reduction of 40% in incidence of neutropenia in the filgrastim group. The analysis was carried out on an intent-to-treat basis. All patients randomised were included in both the efficacy and safety analyses.

Comparisons of duration and incidence endpoints, by treatment group, were made using the Wilcoxon rank-sum test and the chi-square test, respectively. A comparison of event-free survival (disease progression or death) was made for the two treatment groups using the Kaplan–Meier estimation technique and survival curves compared using the log-rank test. Tests of statistical significance were two-tailed with a significance level of 5%.

RESULTS

Patient population

59 patients were recruited from six centres in France between February 1990 and May 1992; 31 were randomised to the filgrastim group and 28 to the control group. Baseline patient characteristics were similar for the two treatment groups (Table 1).

Protocol compliance and on-study events

Chemotherapy dose was reduced for 2 patients (control group) and an accidental 30% chemotherapy overdose was administered to 2 patients (filgrastim group). Chemotherapy was started although patients were thrombocytopenic (filgrastim group, $n=4$; control group, $n=11$), or neutropenic (filgrastim group, $n=2$; control group, $n=11$). 1 patient, randomised to the control group, received filgrastim for 3 days during treatment for febrile neutropenia. 1 patient, (control group) withdrew during course 2 because of disease progression, and 1 patient (filgrastim group), died of septic shock during course 3. A total of 30 and 26 eligible patients completed the study in the filgrastim and the control groups, respectively, and all 59 patients were included in the efficacy and safety analysis, on an intent-to-treat basis (Figure 1).

Efficacy endpoints

The incidence of neutropenia was lower in the filgrastim group after each course of chemotherapy and the difference between treatment groups was statistically significant in courses 2, 3 and 4 ($P<0.01$) (Figure 2). The profile of median neutrophil counts for the two treatment groups is shown in Figure 3. After the first course of chemotherapy, ANCs decreased sharply to a similar nadir in both groups, but recovered more rapidly for patients in the filgrastim group. Similar patterns were observed in later chemotherapy courses, although the nadir was generally less profound, preceded by a rebound of neutrophil counts and recovery occurred earlier in the filgrastim group. As a consequence, the median duration of neutropenia was significantly shorter in the filgrastim group (9 days over the whole study) than the control group (26 days) ($P<0.001$) (Table 2). The reduction in duration of neutropenia was between 4 and 7 days for each course. The incidence of febrile neutropenia was 15–20% lower in the filgrastim group, for each course (Table 3), but this difference was not statistically significant.

The median duration of fever was not significantly different between the two treatment groups; the median total duration of fever over the four courses was 4 days in the filgrastim group and 6 days in the control group ($P=0.12$). The duration of i.v. antibiotic therapy was significantly shorter in the filgrastim group; the median duration was 12 days for the filgrastim group and 20 days for the control group ($P=0.04$). Of the 9 patients not receiving i.v. antibiotics during the study, 7 were in the filgrastim group. The incidence of

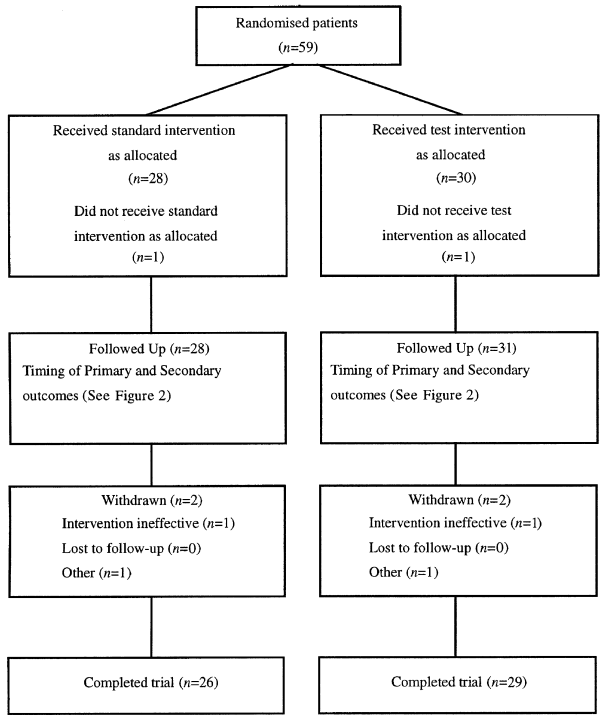

Figure 1. Flow chart of the progress of patients through the trial. (Adapted from Begg C, Cho M, Eastwood S, *et al.* Improving the quality of reporting of randomized controlled trials: the CONSORT statement. *JAMA* 1996, 276, 637–639.)

Table 1. *Patients' characteristics at baseline*

	Filgrastim ($n=31$)	Control ($n=28$)
Age (years)		
Median	3	3
Range	1–10	1–13
Weight (mean in kg)	16.4	15.5
Sex (male/female)	24/7	18/10
ECOG		
0	5	7
1,2	26	21
Primary tumour size*		
1 (≤ 5 cm)	6	4
2 (5–10 cm)	15	15
3 (>10 cm)	8	9
Bone marrow involvement		
Neuroblasts present/absent	28/3	27/1
Abnormal I^{123} MIBG scan	31	28

*Size of the primary tumour was missing for 2 patients in the filgrastim group. ECOG, Eastern Cooperative Oncology Group; MIBG, meta-iodo-benzyl-guanidine.

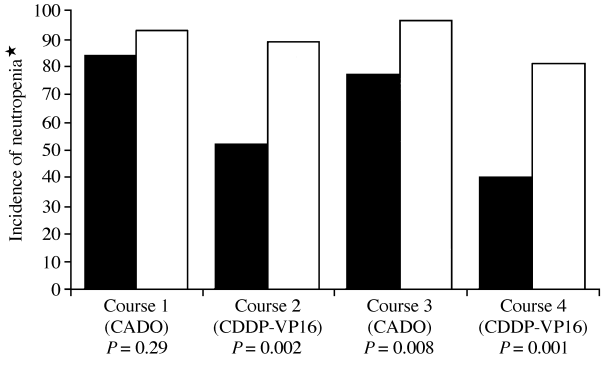

Figure 2. Incidence of neutropenia occurring after each course for the filgrastim group (solid bars) and the control group (open bars). *A patient was deemed to have experienced neutropenia after a course if at least one absolute neutrophil count (ANC) after that course was $<0.5\times10^9$/l.

Table 2. Duration of neutropenia defined as the number of days with absolute neutrophil count (ANC) (or interpolated ANC) $< 0.5 \times 10^9/l$

	Median duration of neutropenia				Median total duration
	Course 1	Course 2	Course 3	Course 4	
Filgrastim					
Median	3	1	2	0	9*
(range)	(0–10)	(0–10)	(0–5)	(0–9)	
Control					
Median	7	7.5	7	4.5	26
(range)	(0–15)	(0–29)	(0–16)	(0.29)	

*$P < 0.001$, based on Wilcoxon test.

Table 3. Incidence of febrile neutropenia

	Number of patients (%)		
Course (chemotherapy)	Filgrastim	Control	*P* value
1 (CADO)	13/31 (42)	16/28 (57)	0.24
2 (CDDP)	5/31 (16)	10/28 (36)	0.08
3 (CADO)	8/31 (26)	12/27 (44)	0.14
4 (CDDP)	1/30 (3)	5/27 (19)	0.06

CADO, cyclophosphamide, vincristine and doxorubicin; CDDP, cisplatin and etoposide.

documented infection was not significantly different between the two groups ($P > 0.05$, each course).

The median duration of non-administrative hospitalisation (defined as all hospitalisation other than days 1–6), although not statistically significant ($P = 0.16$), was 8 days less in the filgrastim group (20 days) than the control group (28 days). There was a significant reduction in the incidence of treatment delays (defined as course length of 24 days or more) in the filgrastim group in courses 2–4 (Table 4). In particular, the median duration of course 2 was 22 days in the filgrastim group (range 20–31) as compared with 25 days in the control group (range 22–38). Over the whole study period, the median duration of treatment was significantly shorter in the filgrastim group (86 days) than the control group (92 days), $P = 0.001$.

Tumour response

The distant metastasis response rate was similar in the two groups, with 25 of 31 patients in the filgrastim group and 19 of 28 in the control group achieving complete or partial remission.

Safety

Two deaths occurred during the observation period. 1 patient (filgrastim group) died during a period of aplasia after the third course of chemotherapy; the cause of death was septic shock related to *Staphylococcus aureus* septicaemia. The second patient (control group) died of metabolic postsurgical complications 23 days after the scheduled end of study. Median event-free survival was longer in the filgrastim group (2.4 years) than the control group (1.3 years), although this was not statistically significant ($P = 0.072$), as shown in Figure 4. By August 1997, 21 of 31 (68%) of patients in the filgrastim group and 23 of 28 (82%) in the control group had progressed or died.

Tolerance to filgrastim was good, with only expected side-effects. The incidence of severe thrombocytopenia (platelet count $< 50 \times 10^9$/l) was similar for the two groups and the need for platelet transfusion support was also similar for the two groups.

DISCUSSION

This was the first controlled study designed to determine the role of filgrastim administration in children receiving combination chemotherapy for newly diagnosed metastatic neuroblastoma. The study demonstrated that s.c. administration of filgrastim significantly reduced the length and severity of neutropenia across the duration of the whole study. As a result of the shorter neutropenia, there was also a significant reduction in the use of i.v. antibiotics. In addition, there were fewer treatment delays in the filgrastim group resulting in a shorter treatment duration compared with control group patients. There was no difference in the incidence

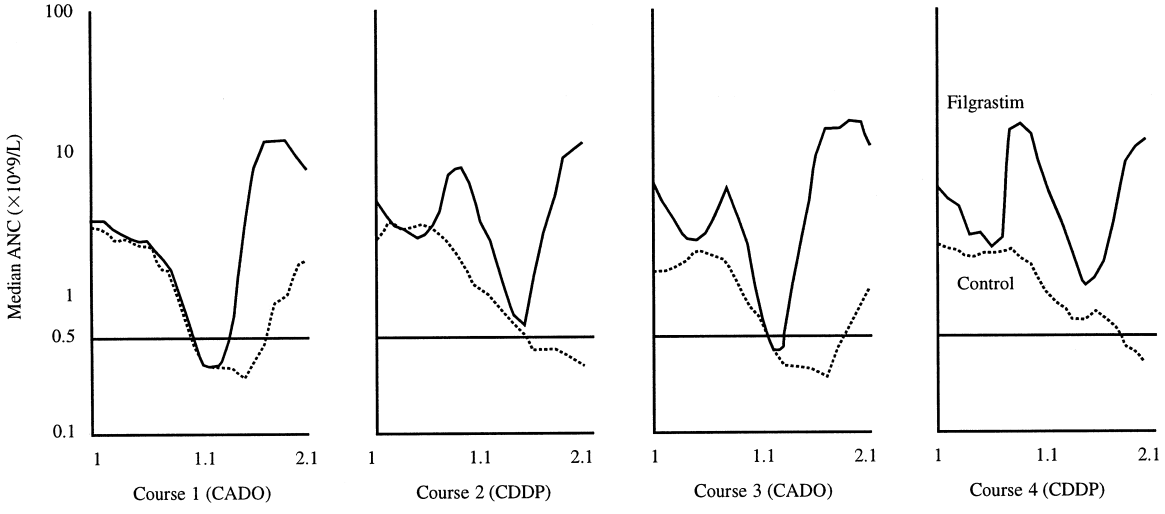

Figure 3. Profile of median neutrophil counts for the control group (solid lines) and the filgrastim group (dotted lines); for median values of absolute neutrophil count (ANC), linear interpolation was used over any period where no ANCs were available.

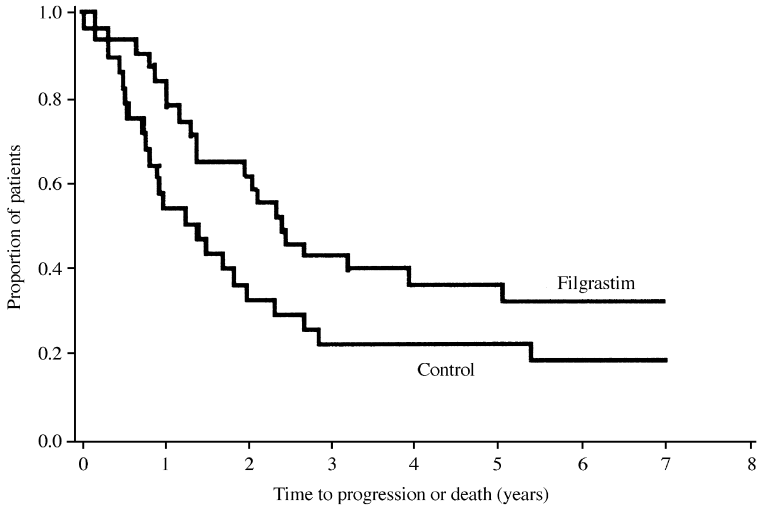

Figure 4. Event-free survival: Kaplan–Meier curves for event-free survival in the two treatment groups are displayed. Median survival times are 2.4 years in the filgrastim group and 1.3 years in the control group, P=0.072 (log-rank test).

of febrile neutropenia or bacteriologically documented infection between the two treatment groups. The duration of hospitalisation was not significantly shortened, probably because there was no effect of filgrastim on causes of hospitalisation not related to neutropenic fever episodes.

The reductions in duration of neutropenia observed over the courses of this study are similar in magnitude to those observed in larger, double-blind studies performed in adults receiving chemotherapy with filgrastim support [7, 8]. The decrease in the incidence of neutropenia over the first cycle of chemotherapy was not significant between the control group and the filgrastim group in this study. Nevertheless, the duration of neutropenia was shortened by 4 days after the first course of therapy for those patients in the filgrastim group which is similar to results observed in large, adult, phase III studies [7, 11]. The lack of a significant effect of filgrastim treatment on the incidence of neutropenia after the first course may be attributable to the heavy bone marrow infiltration at diagnosis, more than to the high alkylating doses used in the CADO combination chemotherapy, since an effect was seen on this parameter after the second CADO, when bone marrow is likely to be less infiltrated. Previously, it has been reported that when higher-doses of cyclophosphamide (7 g/m^2) have been used as a single agent, the incidence of neutropenia has not been modified by the use of recombinant human granulocyte-macrophage colony-stimulating factor (rHuGM-CSF) after chemotherapy, despite a shorter neutropenia duration [12]. The incidence and duration of neutropenia after treatment with CDDP–VP16 (specifically the second course of chemotherapy) were different between the two groups of this study, indicating a treatment effect by filgrastim. This translated into a significant reduction in treatment delays (as per protocol criteria for dosing delays) of 5 days. Similar results to this have been reported when recombinant glycosylated G-CSF (lenograstim) was used after a high-dose cisplatin-containing regimen [13]. In contrast to other studies with filgrastim in adult patients and to one study in children with acute lymphoblastic leukaemia [14], no significant reduction in the incidence of febrile neutropenia, documented infections, or the duration of fever were demonstrated. For febrile neutropenia, there was a consistent trend after each course, with fewer episodes in the filgrastim group. The lack of overall statistical significance for these endpoints may be due, in part, to the comparatively small sample size of this study. The depth of some of the ANC nadirs experienced by patients after CADO chemotherapy was reduced, indicating that filgrastim administration does have the effect of increasing the ANC. It is likely that the profound myelosuppression induced by the CADO chemotherapy when administered to patients whose bone marrow is already compromised by the presence of metastatic disease, serves to expose them to a higher probability of secondary infections.

Table 4. *Incidence of treatment delays after each course*

Course (chemotherapy)	Number of patients (%)		P value
	Filgrastim	Control	
1 (CADO)	4/13 (13)	3/28 (11)	0.80
2 (CDDP)	9/31 (29)	23/27 (85)	< 0.001
3 (CADO)	2/30 (7)	9/27 (33)	0.01
4 (CDDP)	2/30 (7)	12/27 (44)	0.001

CADO, cyclophosphamide, vincristine and doxorubicin; CDDP, cisplatin and etoposide.

In contrast, the significant reduction in the use of i.v. antibiotics in the filgrastim group is directly related to the significant reduction of duration of neutropenia. Guidelines for the administration of antibiotics for this study were so precise that we believe that we were too cautious in our antibiotic usage and hospitalisation of patients at the end of aplasia, thus reducing the possible impact of filgrastim administration on these variables. This is possibly a contributory reason why filgrastim did not affect the number of days of hospitalisation for reasons other than chemotherapy. Children receiving chemotherapy for neoplastic disorders are typically hospitalised for a number of other reasons (not related to monitoring of chemotherapy administration), including reducing the stress from repeated trips to/from hospital for treatment. These will all have been contributory

factors to the hospitalisation of patients in this study, independent of filgrastim use. Therefore, the benefits of filgrastim in reducing chemotherapy-induced morbidity in these patients remains unproven.

Since studies performed in patients with chronic neutropenia have previously shown that chronic administration of doses of filgrastim of between 5 and 10 μg/kg/day were well tolerated in children for long periods of time [15], and given the wide safety and efficacy experience in adult patients receiving 5 μg/kg/day of filgrastim as an adjunct to chemotherapy [7, 8], the dose chosen for this study was 5 μg/kg/day. Unfortunately, neither filgrastim pharmacokinetics nor dose finding studies had been performed in children receiving chemotherapy, before the initiation of this study. It is conceivable that the dose of filgrastim chosen may have been too low to produce measurable clinical effects in a number of clinical parameters. However, even in some adults, filgrastim has been shown to produce clinical effects in haematological variables at doses as low as 1 μg/kg/day [11] and 3 μg/kg/day [6]. Since the initiation of this study, some pharmacokinetic work has been conducted with filgrastim in paediatric patients with neuroblastoma [16], where 5 μg/kg/day dose was found to be effective, but escalation took place up to 15 μg/kg/day. Further, in some settings, doses of filgrastim as high as 10 μg/kg/day have been routinely used [17]. Moreover, recent data in children with acute lymphoblastic leukaemia showing a decreased length of hospitalisation and rate of documented infections, while using a dosage of 10 μg/kg/day, suggest a dose–response effect in the correction of chemotherapy-related infectious episodes in children receiving chemotherapy [18]. The effect of filgrastim on treatment duration was not a major endpoint of this study. Therefore, schedule modifications were not performed for patients recovering to full ANC and platelet counts before day 21 of a chemotherapy course. The median interval between the first CDDP–VP16 and the following CADO course was significantly shorter in the filgrastim group (22 days versus 25 days, $P < 0.001$). From the patients perspective, this has the beneficial effect of allowing a course of chemotherapy to be completed on time and as scheduled, thereby permitting the release of the child from the hospital. Although unmeasured in this trial, this could potentially have a beneficial effect in improving quality of life measures for the child during and immediately after treatment. This may also be of financial benefit because of lower hospital costs. Further, these observed differences could be applied to the clinical situation where other chemotherapy regimens are used in paediatric patients that result in treatment delays. The known effect of filgrastim in reducing treatment delays would allow the optimisation of different treatment regimens with alternating chemotherapy courses to permit maximal dosing with minimal delays in administration. The potential improvement in chemotherapy dose intensity, quality of life and the pharmaco-economic impact of the use of filgrastim warrant further investigation.

No deleterious effects related to filgrastim were seen on the response to chemotherapy at distant metastatic sites or on the survival in this cohort of 31 patients (Figure 4): the proportion of patients whose disease did not regress by the end of induction chemotherapy was lower and the event-free survival higher, although not statistically significant, in the filgrastim group. This could be a reflection of a more timely administration of chemotherapy. As in previous reports in adults [7, 8] and in children [14, 16, 18], filgrastim treatment was well tolerated in this paediatric population, and no deleterious effects were seen on platelets or other haematological or biochemical variables.

In conclusion, filgrastim was a safe adjunct to the combination chemotherapy used for the treatment of metastatic neuroblastoma in this study. For the important clinical parameters of reducing the duration of neutropenia, lessening the severity of the neutropenic nadir, reducing the need for i.v. antibiotics and reducing treatment delays between cycles, the positive benefits of filgrastim have been demonstrated. Given the fact that paediatric tumours often have a high proliferation rate and, therefore, may be more effectively treated by dose intensive chemotherapy, as already demonstrated in neuroblastoma [19, 20] and that filgrastim is a useful adjunct, its role in the treatment of paediatric neoplasms may be of great importance. Further studies are needed to demonstrate that filgrastim, by overcoming chemotherapy related toxicity, may allow a sufficient increase in dose intensity to affect significantly response rate and survival in patients with metastatic neuroblastoma.

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