Dose and outcome: The hurdle of neutropenia (Review)

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Abstract. The development of chemotherapy in the early 1970s resulted in the availability of curative therapeutic strategies for hematological malignancies and several types of solid tumors. It is evident that drugs should be used at their optimal dose and schedule, and drug combinations should be given at consistent intervals. According to the mathematical models that suggested the direct dose-response relationship in the improvement of outcomes in cancer chemotherapy, the dose intensity and, more recently, the dose-dense approach was considered one of the most important tools in conventional chemotherapy. Anticancer drugs are often associated with myelotoxicity, and reducing the dose or increasing the time interval between each cycle of treatment is a frequent empiric approach. Unfortunately, a dose reduction of ≥20% causes a loss of 50% in the cure rate, particularly in chemosensitive tumors. To accelerate bone marrow recovery and prevent the onset of severe myelo-suppression and its complications, the standard use of granulocyte colony-stimulating factors (G-CSF), such as filgrastim and the long-acting pegfilgrastim, is recommended. The aim of this review is to analyze how dose intensification concepts and dose-dense regimens are able to increase the cure rate of chemosensitive solid tumors and lymphomas.

Contents

1. Introduction
2. Study design and methods
3. Has a reduction of dose intensity been detrimental to outcome and are myelotoxic regimens involved in the strategy to achieve a cure?

4. The results on employment of G-CSF or pegfilgrastim to reduce myelotoxicity and maintaining dose intensity
5. 'Dose-dense' chemotherapy
6. Conclusions

1. Introduction

Of the many challenges of medicine, the treatment and curing of cancer in the last 20 years has experienced great progress. The development of chemotherapy in the early 1970s resulted in the availability of curative therapeutic strategies for patients with hematological malignancies and several types of solid tumors. These advances confirmed the principle that chemotherapy could indeed cure cancer and provided the rationale for integrating chemotherapy into combined modality programs with surgery and radiation therapy, chiefly but not exclusively, in the early stages of disease. As research in the medical treatment of cancer progressed, it became evident that drugs should be used at their optimal dose and schedule, and drug combinations should be given at consistent intervals. Moreover, a large number of clinical trials have been designed according to mathematical models that suggested the direct dose-response relationship in the improvement of outcomes in cancer chemotherapy, and dose intensity was considered to be one of the most important tools in conventional chemotherapy (1-4).

The dose-dense approach to increase dose intensity is based on preclinical models of the growth of cancer cells characterized by non-exponential Gompertzian kinetics. In this model, according to the Norton-Simon hypothesis, small tumors grow faster than large tumors. Moreover, the regrowth of cancer cells is a function of cytoreduction, such that the greater the tumor cell kill, the faster the regrowth. This means that cytoreductive chemotherapy will lead to a faster regrowth of cancer cells in the intervals between cycles. Therefore, chemotherapy must be delivered in the shortest possible intervals to be most effective (5).

Because anticancer drugs are associated with side effects, mainly myelotoxicity, it is often appealing for clinicians to avoid acute toxicity by simply reducing the dose or increasing the time interval between each cycle of treatment.

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Such empiric modifications in dose represent a major reason for treatment failure in patients with drug-sensitive tumors who are receiving chemotherapy in either the adjuvant or advanced disease setting; on average, as confirmed in preclinical models, a dose reduction ≥20% gives rise to a loss of 50% in the cure rate (6). To accelerate bone marrow recovery and prevent the onset of severe myelosuppression and its complications, the standard use of granulocyte colony-stimulating factors (G-CSF), such as filgrastim and the long-acting pegfilgrastim, has reduced the incidence and severity of myelotoxicity and made feasible the right therapeutic dose. Pegfilgrastim is a long acting form of filgrastim, created by covalently binding a 20,000 dalton PEG molecule to the N-terminal methionine residue of filgrastim. Pegfilgrastim has a minimal renal clearance, leaving neutrophil-mediated clearance as the predominant method of elimination. This 'self regulating' clearance mechanism makes it possible for the serum levels of pegfilgrastim to remain elevated during CIN and then decline as the ANC recovers.

2. Study design and methods

By using electronic devices and support (PubMed, Medline), we reviewed literature regarding breast cancer, malignant lymphomas, ovarian cancer, soft tissue sarcomas, small cell lung cancer, and germ cell tumors focusing particularly on whether i) if reduction of the dose intensity is detrimental to outcome; ii) if myelotoxicity is an acceptable adverse event when a cure is the main objective of the treatment; iii) if there are results on 'dose-dense' chemotherapy; and iv) if the use of G-CSF (filgrastim or pegfilgrastim) contributes to the cure of chemosensitive tumors by reducing neutropenia, maintaining dose intensity, and allowing dose-dense.

For this review, we considered the standard chemo-therapeutic regimens including G-CSF. Papers published before 1990 were not reviewed unless they were considered historical references.

3. Has a reduction of dose intensity been detrimental to outcome and are myelotoxic regimens involved in the strategy to achieve a cure?

Breast cancer. Among solid tumors, breast cancer represents a challenging topic for two main reasons: the high incidence in Western countries, and the good results achieved by precocious diagnosis and integrated therapies. It is considered a chemosensitive tumor, and laboratory and clinical data show that there is a steep dose-response curve. Thus, dose reduction is associated with the fold-decrease of tumor cell-kill.

The impact of maintaining chemotherapy dose intensity on disease-free survival has been shown in clinical trials of both advanced disease and in an adjuvant setting. In advanced disease, Hryniuk *et al* showed a significant relationship between the dose intensities of combination chemotherapy and response rate in a retrospective analysis (2). This was suggested for CMF as well as for doxorubicin-based regimens. Petit *et al* retrospectively compared the antitumor activity of 5-fluorouracil and cyclophosphamide in combination with either 50 or 100 mg/m² epirubicin, as a neoadjuvant

treatment in stage II-III breast cancer (7). Despite the small number of patients, there was a significantly high response rate in the group receiving the highest dose of epirubicin (82.5% vs. 61.5%). It is worth noting that patients who overexpressed HER-2 and were treated with a high dose of epirubicin had a significantly higher response rate (100.0% vs. 12.5%). Foncan *et al* prospectively compared the anti-tumor efficacy of different dose levels of epirubicin (50 vs. 100 mg/m²) in combination with fixed doses of cyclo-phosphamide and 5-fluorouracil in untreated advanced breast cancer (8). A significant improvement in response rate, response duration and time-to-progression was shown in the group receiving the high dose of epirubicin. Overall survival was similar in the two groups.

In an adjuvant setting, the first clinical evidence was reported by Bonadonna *et al* (9). In a retrospective 30-year follow-up study, they showed that in 1,020 patients treated with CMF in randomized and observational studies, the disease-free and overall survival were significantly superior in the treated group, and in those who had been given at least 85% of the planned dose in this subset of patients (10). Another important study by the French Group demonstrated that high doses of epirubicin given in an adjuvant setting to high-risk breast cancer patients improved the 10-year survival with a satisfactory cardiovascular tolerability (11). These data are in agreement with a retrospective study by the CALGB group reporting on adjuvant chemotherapy in 6,487 patients entered in several trials, including CALGB 8541, and randomized to different doses of adjuvant chemotherapy; the patients treated with high doses had a 12% better chance of remaining alive and disease-free at a median follow-up of 9.6 years than those treated with low dose chemotherapy (12). Maintaining full-dose chemotherapy is often hampered by the occurrence of myelosuppression, with chemotherapy-induced neutropenia being the primary cause of course delays and dose reductions in patients with early-stage breast cancer.

A survey of more than 1,100 patients with operable breast cancer treated at 13 oncology institutions (academic, community practices and managed care) found that 30% of patients received <85% of the standard reference dose. The dose was delayed or reduced in 45% of the patients, and neutropenia was the cause for 61% of these modifications (13). An analysis of more than 20,000 patients with early-stage breast cancer treated with adjuvant chemotherapy found that 35% of the patients had dose reductions of more than 15%, and 25% had treatment delayed more than 7 days. Overall, 56% of the patients were treated with a relative dose intensity of less than 85%, including 67% of those older than 65 years (14).

Non-Hodgkin's malignant lymphomas (NHL). Despite progress in the development of target therapies with the introduction of monoclonal antibodies, chemotherapy remains the mainstay for the treatment of aggressive NHL. About 40% of patients achieve a cure with standard treatments including chemotherapy, plus eventual radiotherapy and/or rituximab. The prognosis and sensitivity to chemotherapy depend upon well-known prognostic factors from the International Prognostic Index being related to clinical and tumor extension parameters. The effectiveness of chemotherapy has been shown to be predicted on the basis of biological features,

Table I. Results for selected regimens in epithelial ovarian cancer.

Regimen	No. of patients	Age (years)	N3/4	G-CSF (days)	FN	Anemia	Plt	Deaths	Reference
Carboplatin+paclitaxel	1,055	19-85	82%	-	NA	7%	11%		Vasey (108)
Carboplatin+docetaxel	1,055	19-85	94%	-	NA	11%	10%		Vasey (108)
PEC dose-dense	22	39-70		6	0	NA	NA	0	Pronzato (109)
Paclitaxel 175	184	Median, 60	NA	NA	22%	7%	5%	NA	Omura (110)
Paclitaxel 250	188	Median, 62	NA	NA	19%	15%	15%	NA	Omura (110)
Topotecan	235	25-85	77%	-	NA	28%	34%	3.8%	Gordon (111)

as defined by a gene expression profile such as CD20 hyper-expression. Furthermore, chemotherapy is widely applied to other types of NHL, i.e. the follicular lymphoma and other rare entities (mantle cell lymphoma, etc.).

As far as aggressive NHL is concerned, the most widely employed chemotherapy regimen is the combination of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP). This regimen is considered myelotoxic, inducing grade 3-4 neutropenia in up to 70% of cases (15-18). Since aggressive NHL is considered chemosensitive, improvements were thought to be achieved by means of chemotherapy intensification; nevertheless, a definitive demonstration of superiority over the CHOP regimen has not yet been reached. In a reference study, it was compared to the so-called second-third generation regimens (MACOP-B, m-BACOD, and PROMACE-CytaBOM) with superimposable results in terms of response, time-to-treatment failure and overall survival, and in favor of CHOP in terms of toxicity; in particular, myelosuppression appears to be higher with these new regimens (19). One theoretical reason for favoring second-third generation regimens is that they are more aggressive and generically more dose intense (i.e. in MACOP-B, the administration of chemotherapy is weekly instead of 3-weekly); on the other hand, dose intensity of cyclophosphamide and doxorubicin is decreased for the concomitant use of other drugs. Therefore, myelosuppression remains the main toxicological problem in treating patients with NHL. This aspect is more important in older patients since the consequences of neutropenia have greater clinical relevance.

A series of studies report that the reduction of dose intensity can compromise the outcome of chemotherapy. A retrospective analysis on the association between the projected dose intensity of 22 studies and the observed response rate showed that increased dose intensity can improve the remission rate (20). Kwak et al observed in a series of 115 patients that a doxorubicin dose intensity of more than 75% was the most important prognostic factor (21). A retrospective analysis showed a long survival in patients that received a >70% relative dose intensity of cyclophosphamide and doxorubicin (22).

Epelbaum et al reported that the prognosis of patients treated with CHOP was significantly different depending on the relative dose intensity applied during the first cycle: the 5-year survival was 80% in patients treated with more than 70% of relative dose intensity and 32% in patients receiving less than 70% (23). A retrospective analysis of 653 patients treated with CHOP or CNOP for intermediate grade NHL showed that 43% of patients received suboptimal chemotherapy and 48% experienced a delay-reduction, usually neutropenia-related, in chemotherapy dose. These dose reductions can affect therapeutic outcomes (24).

Furthermore, the reason that older patients with aggressive NHL have a worse prognosis than younger patients is likely due to the different dose intensity of chemotherapy received. Lee et al demonstrated that patients older than 59 years had a lower 5-year survival than younger ones (30% versus 57%), but this difference was not found in the subgroup of patients treated with a doxorubicin dose intensity of >10 mg/m^2/week (25).

In spite of this evidence, the application of an optimal dose intensity in clinical practice is not always pursued or reached. In a survey of more than 4,500 patients carried out in the USA, a relative dose intensity <85% for CHOP-based regimens was observed in about 50% of patients. An age >60 years, poor PS, advanced disease stage and no prophylactic use of G-CSF were independent predictors of a reduced relative dose intensity; in the same survey, the planned dose intensity was significantly lower in older patients (26). There is strong evidence from these large reviews that more than half of patients with NHL are 60 years or older, and delivery of the standard dose intensity may be particularly troubling in these patients.

Ovarian cancer. Most cases of epithelial ovarian cancer are detected in an advanced stage, and the treatment consists of a combination of aggressive surgery and variously timed chemotherapy. In the rare early presentation, adjuvant chemotherapy is applied after radical surgery. Strong evidence suggests the inverse relationship between chemotherapy effectiveness and the burden of disease.

In the last decade, the regimens applied to ovarian cancer patients are platinum compound-based schemes that range from single agent carboplatin to combinations including cisplatin or carboplatin and cyclophosphamide plus eventual anthracycline, or combinations of cisplatin or carboplatin plus a taxane. After disease relapse, the aim of treatment is palliative as a cure is seldom achieved. However, the regimens employed in this setting (taxane-platinum combinations in 'platinum-sensitive cases,' or topotecan or other agents in 'platinum-resistant cases') are reported to be myelotoxic due to multiple variables such as chemotherapy pretreatment, extension of disease and poor PS.

Table II. Myelotoxic chemotherapies in adult sarcomas: toxicities and outcomes.

Author	Study	No. of patients	Use of G-CSF days (dose)	Grade 3-4 hematological toxicity				Results RR/OS
				Netr. %	Feb. neutr. %	Anemia %	Plt %	
Le Cesne (72)	Random	294	14 (250 μg/m^2/d)	90	16.6	Nd	45	23%
Palumbo (71)	Phase II	39	7 (200 μg)	34	13.0	-	-	59%
De Pas (70)	Phase II	23	8 (5 μg/kg/d)	22 G3 65 G4	35.0	11	10	50%
Reichardt (69)	Phase II	46	10 (5 μg/kg/d)	17 G3 83 G4	54.0	Nd	15 G3 35 G4	52%
Frustaci (74)	Random Adjuvant	104	8 (300 μg/d)	35 G4	11.0 (3rd cycle)	17% G3 3% G4/cy	4 G4	OS>13% (2y) >19% (4y)
Maurel (100)	Phase II	60	10 (5 μg/kg/d)	46	24.0	41	24	38%
Worden (73)	Phase II Random	79	10 (5 μg/kg/dose)	49 SD 87 HD	ND	23 SD 57 HD	10 SD 62 HD	15% SD 21% HD

A retrospective analysis showed a direct relationship between tumor response and relative dose intensity for different regimens (27,28). At least five randomized trials have compared two different doses of cisplatin: no difference in survival was observed in three trials (29-31), while a small but statistically significant difference was observed and there were some concerns about eligibility criteria in the remaining two (32,33).

Regarding the efficacy of carboplatin, a randomized trial compared six courses at area under the curve (AUC) 6 against six courses at AUC 12. In the latter arm, an increase of only 20% instead of the planned 33% of dose intensity was obtained, and no differences were seen in progression-free and overall survival, while the high dose produced more toxicity (34). Similar results were observed in a Danish study comparing AUC 4 to AUC 8 (35).

Regarding paclitaxel, Eisenahuer *et al* compared a bi-factorial design of 135 mg/m^2 with 175 mg/m^2 and 3- or 24-h infusions (36). The response rate was superior for the high dose and prolonged infusion group, but resulted in more neutropenia.

On the basis of these studies, dose intensification up to now has shown poor results. But most studies with platinum compounds were carried out without hematopoietic growth factors, and the toxicity of the higher dose arm was greater, and a reduction of dose intensity was frequently applied with respect to the planned one (Table I).

Adult sarcomas. Adult sarcomas are a heterogeneous group of rare tumors from connective tissues including soft tissue sarcomas (STS), bone sarcomas, and Ewing's family sarcomas. Clinical management involves a multidisciplinary approach including radical local surgery with or without radiotherapy, and systemic therapy. The mainstays of chemotherapy are anthracyclines and oxaphosphorines in which a dose-response relationship was shown for both agents in preclinical models

and clinical experiences. However, responsiveness has a wide range: from absolute refractory in some STS to intermediate-good (bone sarcomas) and high (Ewing's sarcoma) with a real possibility of cure in the last two groups.

Regimens that include ≥70 mg/m^2 of doxorubicin have achieved better responses compared with those using the same drug at lower doses. The combination of ifosfamide and doxorubicin was of particular interest to optimize front-line therapy. Many studies revealed an improved response rate with this combination, but there was no statistically significant difference in survival (37). The major thrust of clinical research has therefore been focused around dose intensification of available agents with the ultimate goal of improving the response rate and quality of response to sufficiently and favorably impact disease-free and overall survival. The major problem with this approach was prolonged, life-threatening myelosuppression. The use of hematological growth factors minimized this side effect.

Table II summarizes the most significant published studies of intensive chemotherapies in different STS. In all phase II studies on the use of intensified chemotherapy in adult sarcomas, the patients received prophylactic G-CSF and this resulted in an overall acceptable hematological toxicity.

Small cell lung cancer. Small cell lung cancer (SCLC) is a clinically aggressive disease with a median survival of only 3 months without treatment, and a significant sensitivity to both chemotherapeutic and radiation therapies. However, maintaining durable response and long-term remission has proved challenging. It has been well defined that patient-related prognostic factors are the stage, ECOG performance status, sex, age, and presence of paraneoplastic syndromes. Assuming that the dose-response relationship plays an important role in this disease, each of these variables can affect the outcome of chemotherapy chiefly by determining the level of toxicities and thus influencing and reducing the planned dose. In fact,

as demonstrated by experimental *in vivo* models, a reduction in dose when the tumor is in the linear phase of the dose-response curve results in the loss of capacity to cure the tumor. Thus, although complete remissions continue to be observed with dose reductions to as low as 20%, residual tumor cells cannot be entirely eliminated, which thereby allows for eventual relapse to occur. Numerous clinical studies have confirmed these laboratory observations.

The combination chemotherapeutic regimens established more than a decade ago remain the standard of care. Two meta-analyses with more than 10,000 patients have found that regimens containing cisplatin and etoposide yielded a survival advantage (38,39).

Retrospective data seem to support a correlation between dose intensity and survival. However, among all studies published in the last 5 years, only the trial of Stewart *et al* showed a significant survival benefit for patients in the intensified arm (40). Also, the shortening of treatment intervals resulted in an improved 2-year survival rate and 3 months in median survival, although there was no significant difference in the response rate and duration of response between treatment groups.

In a randomized phase II study carried out to assess the therapeutic index of two different platinum/etoposide regimens [attenuated-dose (AD) and full-dose (FD) plus prophylactic G-CSF], Ardizzoni *et al* enrolled 95 patients older than 70 years with limited (57%) or extended (43%) SCLC (41). The primary endpoint was the 'therapeutic success (TS),' defined as a patient receiving at least 3 cycles of chemotherapy at the planned dose and schedule, and having an overall response rate without G3 non-hematological toxicity and complications associated with hematological toxicity. The TSs were 10 (36%) in the AD arm and 42 (63%) in the FD arm. All outcome parameters were in favor of the full dose treatment protected by G-CSF. It was concluded that the policy of delivering attenuated doses of an effective regimen appears to provide insufficient therapeutic results in elderly patients with SCLC. All of these results suggest a possible detrimental effect by dose reduction to clinical outcome.

To improve results, additional drugs (epirubicin and cyclophosphamide or ifosfamide) and/or radiation therapy have been combined with PE in phase II and III clinical trials. Compared with the PE regimen, the response rates and survival rates improved in patients with extensive SCLC in the experimental arm (PCDE); however, hematological toxicity was more severe, and toxicity-related deaths were more frequent in the experimental arm (42). These new combinations have shown poor survival improvements in extended-stage SCLC, with a median survival of 9 to 12 months. A promising new chemotherapy combination of irinotecan plus cisplatin was compared with EP in a phase III trial in 154 extended-stage SCLC patients. The study was ended early when a significant survival advantage for irinotecan-cisplatin over EP was observed (median OS, 12.8 vs. 9.4 months, P=0.002; and 2-year OS, 19.5% vs. 5.2%). No severe hematological toxicity was registered in either arm (43). These data were not confirmed at the ASCO Meeting 2005; treatment with weekly IP regimen resulted in no significant differences in overall survival with less myelosuppression and more diarrhea compared with standard EP (44). It is worth noting

that the active drugs given in combination to treat ED SCLC have shown severe hematological toxicities only in poor performance status or elderly patients, and a moderate reduction of dose intensity has been shown to be moderately detrimental in achieving clinical benefit.

On the basis of the concept 'more is better,' the equation of reduced therapy = less clinical results, should be translated into increased therapy = increased clinical results. Unfortunately, this is not the case as it seems doubtful that more toxic regimens can achieve better results.

In a study by the Hellenic Cooperative Oncology Group, 66 patients were divided into two groups to receive a standard or an intensified weekly regimen that increased the doses of carboplatin, epirubicin and ifosfamide by 25%, and the doses of etoposide by 33% given on days 1, 2 and 3 with prophylactic G-CSF support. In the intensified group, the overall response rate was 91.8% (vs. 79.3%), with a 45.9% (vs. 27.6%) complete response rate, a median time-to-progression of 7.05 months (vs. 5.71) and a median survival of 10.16 (vs. 8.3) months. The toxicity was more severe in this group with G3-4 neutropenia in 16% of patients (vs. 0%) and febrile neutropenia with hospitalization of 6% of patients; myelosuppression was the main toxicity, but at acceptable levels. The differences in response rate, time-to-progression and overall survival between the standard and intensified group were not statistically significant (45).

More significant advances have been seen in limited-stage disease. In combination with conformational radiation therapy, platinum-based regimens have produced a median survival time of 20 months, with 20% of patients achieving a durable remission at 5 years (46). The effect of scheduling combined radio-chemotherapy was studied in randomized trials to define the best sequence; a meta-analysis of 6 studies, with 2-year survival as the endpoint, demonstrated a trend towards long survival in the group in which early radiotherapy was given concurrently with chemotherapy. Hematological toxicity was increased, and any decrease in dose intensity should be avoided by the introduction of hematological growth factors (47,48).

Germ cell tumors. Germ cell tumors still represent a unique model of curable solid tumors even with the presence of advanced disease (49). These outstanding results were obtained for two main reasons: the peculiar sensitivity of the tumor cells to some antineoplastic agents (mainly cisplatin), and a rational algorithm of treatment i.e. the right drugs and right schedules at the right time.

The 'quantity' of treatment depends on the prognostic category according to the IGCCCG classification (50). In patients with a good prognostic score, three courses of cisplatin, etoposide and bleomycin (BEP) is considered the standard first-line option given on either a 3- or 5-day schedule, while four courses of the same schedule are mandatory for more aggressive cancers (intermediate and poor risk categories).

The role of dose intensity is well recognized in achieving the goal of curing sensitive cancers such as advanced germ cell tumors. However, the impact of major schedules on neutropenia is well known as the first- and second-line therapy in this disease. It has been reported that up to 30-50% of patients are not able to receive a full-dose treatment

Table III. Prophylactic use of filgrastim in breast cancer adjuvant treatment.

Author	Patients	CSF	Planned dose on time <85%	Hospitalization for febrile neutropenia	Febrile neutropenia	Other G3-4 toxicities
Rivera (56)	360 HR (≤500 ANC)	G-CSF from day 2	12.1%	4.4%	11.1%	NA
	264 LR (>500 ANC)	to ANC ≥10,000/ml	4.2%	0.8%	2.6%	
	358 matched controls		5.6%[a]	4.7%	9.4%	
Martin (58)	115 TAC+G	G-CSF	NA	NA	3.5%[a]	20.0%[a]
	109 TAC				23.8%	50.4%
	224 FAC				1.3%	26.7%
Roché (59)	100 FEC x6	G-CSF, if required	NA	NA	1.6%	NA
	100 FEC x3→DCT x3				2.5%	

[a]Same as Table VII. NA, not applicable.

because of myelosuppression (51). Another schedule employed in the treatment of germ cell tumors was the combination of vinblastine, cisplatin, and ifosfamide (PVB) (52). This schedule was evaluated in the pre-growth factor era, and the rate of grade 4 neutropenia was close to 60%. The chemotherapy schedule of VeIP (combination of vinblastine, ifosfamide, and cisplatin) was employed in the late 1980s with good results in seminoma and non-seminoma. Without the use of growth factors (unavailable at that time), the percentage of patients developing grade 4 leukopenia was as high as 50% with a possible 30-40% of patients developing grade 4 neutropenia.

A new dose-intense regimen is now being tested and consists of the combination of bleomycin, vincristine and cisplatin (BOP), alternating with bleomycin, etoposide and cisplatin (BEP), for a total of three BOP/BEP administrations (53). According to protocol, the administration of colony-stimulating factors was not allowed, and it was left to the treating physician's discretion if neutropenia or neutropenic complications arose. Ninety percent of the patients developed either grade 3 or 4 neutropenia (grade 4 in 83%). Thirteen patients were hospitalized a total of 18 times due to neutropenic complications. Moreover, 5/43 patients were treated with G-CSF for prolonged neutropenia. The results of this phase II dose intense regimen were impressive (81% overall survival and 72% progression-free survival). For a population with an intermediate-poor prognosis, the addition of upfront G-CSF considerably reduced the risk of major neutropenia and neutropenic complications.

4. The results on employment of G-CSF or pegfilgrastim to reduce myelotoxicity and maintaining dose intensity

Breast cancer. Silber *et al* developed a risk model for neutropenic complications in patients with early-stage breast cancer treated with adjuvant chemotherapy (54). They found a significant relationship between the depth of absolute neutrophil count nadir in cycle 1 (ANC ≤500/μl vs >500/μl) and subsequent neutropenic complications. The model has been validated in both retrospective and prospective studies

(55,56), which predicted the likelihood of reducing the dose intensity of chemotherapy to less than 85% (55% with ANC nadir ≤500/μl vs. 32% with ANC nadir >500/μl) and confirmed the role of hematological growth factors in increasing the rate of delivering dose intensity.

A meta-analysis of the results from 8 randomized controlled trials of G-CSF vs. placebo found that chemotherapy dose reductions or delay were doubled in patients receiving the placebo. The use of G-CSF decreases the likelihood of neutropenic complications in both the initial and subsequent cycles of therapy (57). The prophylactic use of G-CSF on febrile neutropenia after the docetaxel, doxorubicin and cyclophosphamide (TAC) regimen was assessed in an interim safety analysis of the GEICAM 9805 study. The TAC regimen (vs. conventional FAC regimen) has been shown to improve disease-free and overall survival in node-positive breast cancer, but at a higher rate of febrile neutropenia (Table III). The GEICAM 9805 studies compared 6 cycles of 3-weekly TAC vs. 6 cycles of 3-weekly conventional FAC in high-risk node-negative breast cancer (58,59). A first group of patients (109 patients) treated with TAC did not or only occasionally received prophylactic G-CSF. Subsequently, the study was amended and a second group (115 patients) received G-CSF beginning with the first cycle of TAC. Within the limitations of a non-randomized comparison, the incidence of febrile neutropenia was substantially lower in the group receiving G-CSF (3.5% vs. 23.8%). Moreover, the rate of other G3-4 toxicities was consistently lower in the group receiving G-CSF (20.5% vs. 50.4%).

Two randomized phase III trials that compared G-CSF, filgrastim and pegfilgrastim in patients with breast cancer treated with docetaxel and doxorubicin (Table IV) found that pegfilgrastim was comparable to filgrastim in reducing the incidence of febrile neutropenia and duration of grade 4 neutropenia (60,61).

One study tested pegfilgrastim in a double-blind, placebo-controlled phase III study in breast cancer patients treated with docetaxel in both metastatic and non-metastatic disease. Pegfilgrastim markedly reduced febrile neutropenia, the frequency of hospitalizations and use of antibiotics (62).

Table IV. Comparison of pegfilgrastim versus placebo or G-CSF in breast cancer patients.

Author	Patients	Treatment	G-CSF	Comments
Holmes (60)	Pegfilgrastim, 154 G-CSF, 156	Docetaxel 75 mg/m^2+ doxorubicin 60 mg/m^2, x4 cycles	Pegfilgrastim on day 2 of each cycle, G-CSF from day 2 to ANC ≥10,000/ml	Pegfilgrastim was safe and effective as daily Filgrastim in reducing neutropenia and its complications.
Green (61)	Pegfilgrastim, 77 G-CSF, 75	Docetaxel 75 mg/m^2+ doxorubicin 60 mg/m^2 x4 cycles	Pegfilgrastim on day 2 of each cycle, G-CSF from day 2 to ANC ≥10,000/ml	Pegfilgrastim was safe and effective as daily Filgrastim in reducing neutropenia and its complications.
Vogel (62)	Pegfilgrastim, 463 placebo, 465	Docetaxel 100 mg/m^2, q 3 weeks	Pegfilgrastim 6 mg or placebo on day 2 of each cycle; if FN can cross to pegfilgrastim in placebo arm	Naïve and pretreated patients; chemotherapy moderately myelo-suppressive; pegfilgrastim markedly reduced febrile neutropenia.
Von Minckwitz (112)	Cohort A, 390 cohort B, 323 cohort C, 236	Docetaxel 75+ doxorubicin 50+ cytoxan 500 mg/m^2; q 21 days x 6-8 cycles	A) Filgrastim from day 3 to 12; B) Pegfilgrastim on day 1 or 2; C) Pegfilgrastim on day 1 or 2+ ciprofloxacin 500 mg b.i.d. on days 5-14	Neutropenia and infections during neoadjuvant TAC can be avoided by primary prophylaxis with pegfilgrastim+ciprofloxacin.

Non-Hodgkin's malignant lymphoma (NHL). Studies specifically carried out in patients with aggressive NHL examined the impact on myelotoxicity and dose intensity.

A randomized clinical trial in patients over 60 years has shown that the prophylactic use of G-CSF reduces the risk of complications due to neutropenia in patients receiving CHOP or CNOP (63). In this trial, a slight difference in delivered dose intensity was registered likely due to the favorable selection of patients, but a difference was not observed in complete remissions or overall survival. In a second study, the addition of G-CSF to CHOP resulted in a higher delivered dose intensity without affecting survival outcome; the cumulative days on antibiotics were fewer in the CHOP plus G-CSF arm, but the incidence of febrile neutropenia was not significantly lower (37.5% vs. 44.0%) (64). Notably, the relative dose intensity of cyclophosphamide and doxorubicin in the two arms was higher with and without G-CSF (about 90%). In other words, it should be considered that patients likely to receive a lower dose intensity (at a level able to compromise clinical outcome) were not admitted to this study. Other randomized studies have shown that the prophylactic use of G-CSF is associated with dose intensity maintenance for different chemotherapy regimens. However, the use of prophylactic G-CSF did not reduce the occurrence of non-hematological toxicities, use of antibiotics or frequency of hospitalizations (65), and the higher dose intensity does not raise the CR rate or provide a more durable remission (66).

Pegfilgrastim has been employed in a randomized phase II study in which patients receiving etoposide, cisplatin, cytosine, arabinoside and prednisone were randomized to pegfilgrastim (one administration of 100 µg/kg) or filgrastim (daily administrations of 5 µg/kg) (67). Toxicity and tolerability were similar for both treatments. In a phase II study, Grigg *et al* randomized elderly patients to 60 or 100 µg/kg pegfilgrastim or 5 µg/kg filgrastim daily from day 2, or no G-CSF after the first cycle of CHOP. After balancing risk factors between the 4 arms, 100 µg/kg pegfilgrastim and filgrastim yielded similar results for the duration of grade 4 neutropenia, which were assumed in the primary endpoint of the study, and remained far longer in the no treatment arm. Interestingly, the cumulative number of G-CSF injections was 6 for pegfilgrastim and 60 for filgrastim. A full dose of cyclophosphamide and doxorubicin was delivered to 94% of patients in the filgrastim arm, 98% of patients in the 60 µg pegfilgrastim arm and 100% of patients in the 100 µg pegfilgrastim arm (68).

Adult sarcomas. Studies that used higher doses of anthracyclines or ifosfamide in combination chemotherapy with G-CSF support achieved a higher response rate in the range of 42-67%. In a phase II study, Reichardt *et al* reported a response rate of 52% with a complete response rate of 22% in patients treated with a high-dose ifosfamide regimen and G-CSF support (10 days); all patients experienced grade 3-4 myelosuppression with a febrile neutropenia rate of 54% showing that, although toxic, this regimen is feasible and produces a high number of partial and complete remissions (69).

Table V. Dose intensification chemotherapy studies on Ewing family tumors.

Trial	No. of Pts	Age	Neutr G3/4%	N d	Use of G-CSF days (dose)	FN %	Anemia %	Plt %	Tox	R
Marina (75)	53	13.4	In: 98 Main: 100 SD 83 HD	In: 17 Main 49	10-14 (10 μg/kg/dose)	In: 89 Main: 75 SD 89 HD	Nr	In: 91 Main: 100 SD 93 HD	Nr	CR 82%, PR 16%, 3-year 72%, EFS 60%
Felgenhauer (76)	24	10.5	94 (of courses)	Nr	Nr (5-10 μg/kg)	81	84 (of courses)	90	Nr	CR 54%, TTP 15.6 m, 2-year EFS 50%
Womer (103)	71	11	In: 17 Main 49	Nr	Nr (5 μg/kg/d)	In: 38 (cy) Main 7 (cy)	Nr	In: 19 (cy) Main 45 (cy)	1 (In)	NA

Pts, patients; plt, platelets; in, intensification treatment; main, maintenance treatment; SD, standard dose; HD, high dose.

In a phase II non-randomized trial with 23 patients, De Pas *et al* studied the feasibility of a chemotherapy regimen with high-dose ifosfamide plus adriamycin followed by G-CSF support in the treatment of advanced soft tissue adult sarcoma and observed a response rate of 50% (70). Twenty-three patients received 89 cycles of chemotherapy and 70 cycles were at full dose; the incidence of G3 and G4 neutropenia was 22% and 65%, respectively, and febrile neutropenia occurred in 35% of patients, with four of them requiring hospitalization. However, the data were inconclusive on the efficacy of this treatment because of heterogeneity and a limited population.

In a phase II study on 39 patients treated with an intensive epirubicin/ifosfamide schedule, Palumbo *et al* showed a CR and PR rate of 13% and 46%, respectively. Neutropenia was the most relevant hematological toxicity; 73% of chemotherapy courses were associated with neutropenia of all grades, but only 13% of patients had grade 4 and the incidence of febrile neutropenia was 13% (71).

Activity of a high-dose doxorubicin-containing regimen was compared with a conventional standard-dose regimen in adult patients with advanced soft tissue sarcomas (72). Objective responses were observed in 21% of patients in the intensified arm and 23% of patients in the standard-chemotherapy arm (not significant), which did not confirm the expected dose-response relationship despite a 50% increase of doxorubicin dose intensity in the arm of high-dose chemotherapy. Hematological toxicity was the most frequent side effect, with grade 3-4 neutropenia documented in 92% of patients in the standard arm and 90% in the intensified arm, and a higher incidence of febrile neutropenia in the intensified arm (16.6% vs. 4.6%, P=0.0004).

In a randomized phase II study, Worden *et al* compared the efficacy and toxicity of fixed dose doxorubicin in combination with high- or standard-dose ifosfamide in 79 patients with STS (73). Both arms were supported with prophylactic G-CSF. The authors concluded that this approach did not improve clinical results (1-year DFS), and toxicity was greater than expected in the intensified arm.

In the last 5 years, the role of intensified chemotherapy on STS in an adjuvant setting was examined in only one trial by Frustaci *et al* (74). In this study, 104 patients with grade 3-4 spindle cell sarcoma were randomized after surgery to receive adjuvant treatment with 5 cycles of 60 mg/m^2 epirubicin on days 1 and 2, and 1.8 mg/m^2 ifosfamide on days 1-5 with prophylactic G-CSF versus the control arm. The median survival time was higher among patients who underwent adjuvant therapy (75 months) compared with untreated patients (46 months); the risk reduction in treated patients was statistically significant (P=0.03) and the absolute improvement derived from chemotherapy was 13% at 2 years and 19% at 4 years. Although a cure is still difficult to achieve in adult STS, a significant delay in death is worthwhile, considering the short duration of treatment and absence of toxic deaths.

The Ewing's family of tumors consists of bone and soft tissue sarcomas that primarily affect children and young adults. The consistent use of multimodality therapy, including intensive chemotherapy, radiation therapy and surgery, has improved the survival of patients with localized sarcomas but, despite high complete remission rates, has not modified the prognosis among patients with metastatic disease at diagnosis.

In a study published in 1999, Marina *et al* treated 53 patients with both advanced and localized disease, with a sequence of surgery, induction CT (3 cycles of ifosfamide/etoposide on days 1 to 3 and cyclophosphamide/doxorubicin on day 5 followed by G-CSF), local control with surgery and/or radiotherapy started at week 9 along with vincristine/dactinomycin, and maintenance CT (4 alternating cycles of ifosfamide/etoposide and doxorubicin/cyclophosphamide at standard or high dose, followed by G-CSF) (75). Patients were randomized to two different cytoxan (CTX) maintenance schedules, standard dose (SD: CTX 1 g/m^2/d x2) or high dose (HD: CTX 1.5 g/m^2/d x2). During induction therapy, 98% of

Table VI. Impact of neutropenia in the treatment of germ cell tumors (no growth factors).

Schedule	GN grade 4 (%)	Febrile neutropenia (%)	Reference
BEP	13	13	51
VIP-B	49	46	51
PVB	59	NR	52
VeIP	NR	86	113
PEI	30-50	26	80
BOP/BEP	83	28	53

patients developed grade 4 neutropenia with 89% of patients requiring hospitalization for febrile neutropenia. During the maintenance phase, grade 4 neutropenia was present in 100% of patients in the standard arm and 93% of patients in the intensified arm (75% and 80% of patients had febrile neutropenia, respectively). The patients achieved an excellent response to therapy with 82% CR (86% SD and 78% HD), 16% PR, and 3-year survival and EFS rates of 72%±8% and 60%±9%, respectively. This study suggests that a dose-intensifying treatment is feasible in all patients before the administration of local therapy, but only in a minority of patients after radiotherapy. Moreover, no significant benefit using an HD approach was achieved.

In a small study by Felgenhauer *et al*, 24 patients with metastatic disease received eight courses of VACIME chemotherapy (2 mg/m^2 vincristine on day 0, 20 mg/m^2/d doxorubicin on days 0-3; 360 mg/m^2/d cyclophosphamide on days 0-4; 1800 mg/m^2/d ifosfamide on days 0-4 and 100 mg/m^2/d etoposide on days 0-4 with G-CSF after each course). In the 7th and 8th course, doxorubicin was withdrawn (76). Surgical resection followed course 6 and radiotherapy followed the completion of all therapy. Grade 3-4 neutropenia was observed in 94% and febrile neutropenia in 81% of all cycles. Fifty-four percent of patients achieved CR after chemotherapy alone, the median time to recurrence was 15.6

months, and the 2- and 4-year EFS were 50% and 45%, respectively, suggesting that increased dose intensity improves the response rate in paediatric sarcomas, although the improvement in survival is less certain (Table V).

Small cell lung cancer. The impact on survival by shortening chemotherapy intervals has also been tested. In a trial by Steward *et al* in which 299 patients were randomized to 6 cycles of V-ICE every 3 or 4 weeks (standard and intensified arm, respectively); a second randomization was made to GM-CSF or a placebo (77). The incidence of grade 4 neutropenia was higher in the experimental arm (59% vs. 49%), but GM-CSF reduced the frequency of grade 4 neutropenia within each of these arms. Febrile neutropenia occurred in 54% of all patients, and there was no significant difference in the incidence between the two groups. The median duration of hospitalization was 12 days in the GM-CSF group and 13 days in the placebo group. There was no significant difference in the response rate or duration of response between treatment groups; there was a significant survival benefit for those in the intensified arm (443 vs. 351 days). The dose intensity treatment resulted in a 15% improvement in the 2-year survival rate (P=0.0014).

In another large randomized trial, 403 patients received 6 cycles of ACE chemotherapy every 3 weeks (control group) or every 2 weeks with G-CSF support (DI increased by 50% in the experimental group). Neutropenia G2-4 occurred in 21% of patients in the intensified arm with 33% treated with antibiotics, versus 83% in the control group with 34% of patients treated with antibiotics. Reported deaths from myelo-suppression occurred in 6 patients in the intensified arm and 8 in the standard arm. In the experimental and control groups, CR was 40% and 28% (P=0.02) with a total response rate of 78% and 79%, respectively; survival rates were 47% and 39% at 12 months and 13% and 8% at 24 months (78).

Germ cell tumors. All regimens employed in the treatment of germ cell tumors are characterized by significant myelotoxicity (Table VI), which interferes with efficacy. The ASCO 2000 update recommendations suggest the use of hematopoietic colony stimulating factors in such curable disease after a

Table VII. Phase II randomized trials of dose-dense neoadjuvant chemotherapy.

Author	Patients	Treatment	G-CSF (days)	BCS %	pCR %	pN- %
Untch (83)	631	E 150 x3, T 250 x3 for q 2 weeks	3-10	66.0[a]	18.0[a]	51.0[a]
		E 90 +T 175 x 4 for q 3 weeks		10.0	10.0	42.0
Green (84)	258	T weekly x 12, FAC x 4	None	NR	28.8[a]	
		T 3 weeks x 4, FAC x 4			13.6	
Jackisch (82)	395	AD x 4 q 2 weeks	5-10	65.5	7.1	55.4
	913	AC x 4 q 3 weeks		74.9	14.1[a]	60.7
Euler (81)	151	EC x 3 q 2 weeks	NR	81.5	3.9	
		EC x 3 q 3 weeks		80.0	9.5[a]	

A, doxorubicin; E, epirubicin; T, paclitaxel; D, docetaxel; C, cyclophosphamide; BCS, breast conservative surgery; pCR, pathological complete response; pN, pathological nodal status. [a]Statistically significant, mg/m^2.

Table VIII. Dose-dense adjuvant chemotherapy for high-risk resectable breast cancer.

Author	No. of patients	Study	Treatment	G-CSF	mDI %	Comments
Venturini GONO (88)	1,214	Ph III	FEC x 6 q 2 weeks FEC x 6 q 3 weeks	NR	93 94	Non-significant reduction of HR of death on DD arm
Hudis (91)	42	Ph II	A x 3, T x 3, C x 3 q 2 weeks	3-10	92	Feasible and promising treatment
Fornier (85)	42	Ph II R	A x 3, T x 3, C x 3 q 2 weeks A x 3, - TC q 2 weeks	3-10	98 87	Increased toxicity on DD arm: hospitalization, febrile neutropenia, incidence of RBC transfusions
Citron (90)	2,005	Ph III 2 x 2	A x 4, T x 4, C x 4 q 2 weeks A x 4, T x 4, C x 4 q 3 weeks AC x 4, T x 4 q 2 weeks AC x 4, T x 4 q 3 weeks	3-10 3-10	NR	Dose-density significantly improves DFS and OS; DD decreases neutropenia
Mobus (89)	1,169 1,284	Ph III	E x 3, T x 3, C x 3 q 2 weeks EC x 4, T x 4 q 3 weeks	3-10	82 90	Dose-density significantly improves DFS and OS; DD increases haematological toxicity

A, doxorubicin; E, epirubicin; T, paclitaxel; C, cyclophosphamide; mDI, median dose intensity.

previous episode of febrile neutropenia, and discourage the reduction of cytotoxic drugs (79).

At the present time, G-CSFs are employed in the treatment of germ cell tumors to maintain dose intensity (i.e. the right therapy at the right time) and allow intensified schedules. As dose intensity is a pillar of successful chemotherapy in advanced germ cell tumors, centers such as Indiana University are now using G-CSF as the primary prophylaxis for intermediate and poor risk patients for each of the 4 cycles of BEP (80).

5. 'Dose-dense' chemotherapy

Breast cancer. The pharmacological hypothesis of dose-dense chemotherapy was initially investigated in 4 randomized phase II studies whose results were controversial (Table VII): there was no evidence of better outcomes in two studies (81,82), and significantly greater pathologic complete response plus a higher percentage of breast conservative surgery and pathological negative nodes in the other two (83,84). However, a benefit of dose-dense chemotherapy was confirmed by Fornier *et al* (85). Two additional phase III trials tested the dose-dense neoadjuvant chemotherapy in locally advanced breast cancer with hematological growth factor support, but no measurable therapeutic benefits were demonstrated (86,87). In an adjuvant setting, a dose-dense approach has been investigated in phase II and III clinical trials in patients considered at high risk of recurrence (Table VIII).

The effect of dose-dense chemotherapy was tested in three large prospective phase III studies: two presented in abstract form (88,89), and the third was a CALGB (C9741) trial that compared sequential A-T-C with concurrent doxorubicin and cyclophosphamide followed by paclitaxel (AC-T) using dose-dense (2-weekly) or conventional (3-weekly) schedules as adjuvant chemotherapy in 1973 patients with breast cancer (90). The dose-dense schedule was possible by using G-CSF. The dose-dense regimens resulted in significantly longer 3-year disease-free survival (85% vs. 81%) and 3-year overall survival (92% vs. 90%), regardless of predictive factors. There was no difference in disease-free survival or overall survival between the sequential and concurrent arms. Grade 4 neutropenia was more common with conventional therapy, occurring in 33% of patients treated with conventional regimens and 6% of those receiving dose-dense regimens (p=0.0001). Moreover, the number of courses delayed because of hematological toxicity was lower in the dose-dense arm than in the conventional schedule arm (15% vs. 38%). Furthermore, dose-dense chemotherapy significantly reduced the occurrence of contra lateral breast cancer (0.3% vs. 1.5%). CALGB 9741 showed not only the feasibility of this approach, but also the superiority of dose-dense over conventional chemotherapy (91).

Non-Hodgkin's malignant lymphoma (NHL). The issue of dose-dense chemotherapy was also addressed in patients with aggressive NHL. The 'dose-dense approach' appeared feasible in different studies (92,93), and preferable to increasing the dose per cycle, although maintaining the 14-day interval and G-CSF support means that increasing the dose of cyclophosphamide can be attempted (94).

The German High-Grade NHL Study Group demonstrated that patients aged over 60 receiving CHOP every 14 days fared better in time to treatment failure and overall survival compared to patients receiving CHOP at the standard 21-day interval (95). The same hypothesis was also evaluated in

Table IX. Comparison between two different schedules of CHOP and CHOEP ± G-CSF.

	CHOP 21	CHOP 14	CHOEP 21	CHOEP 14
Adriamycin dose intensity, mg/m²/week	97% x 16.6	93% x 25	96% x 16.6	83% x 25
Complete remission rate	60.1%	76.1%	70.0%	71.6%
5-year event-free survival	32.5%	43.8%	41.1%	40.2%
5-year overall survival	40.6%	53.3%	45.8%	49.8%
Patients requiring RBC transfusion	24.6%	40.2%	39.2%	64.3%
Patients requiring platlet transfusion	1.7%	3.6%	9.0%	15.5%
Patients requiring antibiotics	37.9%	48.2%	60.6%	62.5%

CHOP and CHOEP 14 were given with G-CSF. RBC, red blood cells.

younger patients who were randomised and given CHOP or CHOP-etoposide every 14 or 21 days. A survival advantage for the shorter interval was observed, and the addition of etoposide resulted in a higher complete response rate and longer 5-year event-free survival. Interestingly, the chemotherapy acceleration with G-CSF did not increase non-hematological toxicity in these studies (Table IX). The duration of G-CSF treatment in the above-mentioned studies ranged from 6 to 10 days; in studies by the German High-Grade NHL Study Group, the duration was initially established in 10 days, and an attempt to reduce the treatment duration was made by the same group (96). Kloess *et al* compared the data of elderly patients that entered a new trial with CHOP plus G-CSF administered for only 7 days with the results of the previous trial with 10 days of G-CSF; the reduced dose allowed the accelerated administration of CHOP, but the rate of infections doubled from 2.4% to 5.2% (97). Moreover, two trials demonstrated the feasibility of the dose-dense approach employing pegfilgrastim instead of filgrastim. In these two studies, CHOP was administered every 14 days with pegfilgrastim (or filgrastim in one of them) with similar results in the application of the dose-dense chemotherapy (98,99).

Adult sarcomas. In the only published study in which dose-dense chemotherapy was employed, Maurel *et al* treated 57 chemotherapy-naïve patients with unresectable locally advanced or metastatic adult STS with doxorubicin for 3 days and a continuous infusion of ifosfamide over 5 days every 21 days, for 3 cycles with G-CSF for 7 days (100). Grade 3-4 neutropenia and febrile neutropenia were found in 46% and 24% of patients, respectively; there were no treatment toxicity-related deaths. After the completion of therapy, the overall response rate was 38% with a median time-to-progression of 24 weeks. Compared with the dose intensity schedules used in other trials, the current regimen had reduced toxicity in terms of G3-4 neutropenia and febrile neutropenia with a similar clinical efficacy.

Significant studies on the dose-dense treatment of Ewing's family sarcoma tumors have been published. The expected survival rate is between 70-80% in patients with locally advanced disease, while the clinical outcome for patients with metastatic disease is highly improved in comparison with past results, but still unsatisfactory. Many studies are exploring the use of high-dose chemotherapy with the rescue of peripheral blood progenitor cells (101,102).

Womer *et al* conducted a prospective study in 73 children and adolescents with both localized and advanced Ewing's family sarcomas to determine whether G-CSF permits dose intensification (103). The alternated vincristine-doxorubicin-cyclophosphamide and ifosfamide-etoposide regimens, with G-CSF between courses were given in two phases (6 cycles of induction and 6 cycles of maintenance), and included primary tumor treatment with surgery and/or radiotherapy. Neutropenic fever occurred in 38% of induction cycles and 26% of maintenance cycles. This treatment was well tolerated and produced excellent results, showing the feasibility of the dose-dense approach.

Small cell lung cancer. Because of the high growth rate of SCLC, dose-intensive chemotherapy should theoretically have an impact on survival. However, after many years and several clinical trials, dose-intensive chemotherapy has failed to produce significant improvements in survival for these patients (104).

In a prospective multicenter phase III study examining the impact on overall survival of dose intensity and dose density, 244 patients with limited or extensive SCLC were randomised to receive standard CDE or intensified CDE with G-CSF (increase of dose by 25%, DD by 33% and DI by 90%). Myelosuppression was more severe in patients treated within the intensified arm with an overall incidence of grade 3 or 4 leukopenia similar in the two arms (over 90%) and grade 4 leukopenia in 50% and 79% of patients in the standard and intensified arm, respectively. Febrile neutropenia occurred in 24% of patients treated with standard doses versus 34% of patients treated with intensified CDE (P=0.102) with the 3% and 5% toxic deaths, respectively. In terms of response, there was no significant difference between the two arms; the overall response was 79% in the standard group and 84% in the intensified group, with 25% and 21% CR, respectively. After a median follow-up of 49 months for patients on the standard arm and 57 months for patients on the intensified arm, 90% and 87% have died (105).

In May 2005, Lorigan *et al* reported their phase III trial of standard ICE (4-week interval) versus dose-dense ICE (2-week interval) supported by 10 days of filgrastim and autologous blood recorded the day before the cycle and reinfused 24 h from the end of chemotherapy (106). The role of this autologous blood support does not appear to interfere with hematological recovery, in fact the granulocytopenia was

significantly worse in the dose-dense arm. However, the authors suggest that the levels of natural killer cell precursors may be maintained in autologous salvaged blood, and this should justify why fewer patients in the dose-dense arm had febrile neutropenia. The conclusions of this trial are that dose-dense ICE with G-CSF and autologous blood transfusion shortens the treatment duration and reduces the occurrence of febrile neutropenia, but does not statistically improve overall survival, response rate or 2-year survival.

6. Conclusions

The results of this overview have confirmed that the role of chemotherapy and the maintenance of its doses and schedules are still of great importance, particularly in the so-called chemosensitive tumors. Hematological toxicity remains the main cause of dose reduction or course delay, and the reduction of dose intensity consequently and negatively affects clinical outcome. Hematopoietic growth factors such as granulocyte colony-stimulating factor (G-CSF), filgrastim and pegfilgrastim, are a family of cytokines that regulate the proliferation, differentiation, and viability of hematopoietic progenitor cells and mature blood elements. Overall, the ability of G-CSF to enhance hematopoiesis is widely used as part of treating certain cancers and has led to improved safety of high-dose chemotherapy.

Breast cancer treatments have been carefully reviewed, looking at the relationship between dose intensity and clinical response to chemotherapy. There is a wide debate about the concept that a reduction of dose intensity below 85% of the planned dose is detrimental in adjuvant and metastatic settings. The occurrence of myelotoxicity is strictly related to the characteristics of the employed regimens, including the interval between cycles. However, in standard schemes, neutropenia and febrile neutropenia are not generally so severe and prolonged to compromise the safety of the patient, but enough to induce dose reduction in a large percentage of patients, particularly older patients, thus influencing the final clinical results. The preventive use of G-CSF according to well-defined international guidelines overcomes the problem, and permits the maintenance of planned dose intensity. As far as dose-dense regimens are concerned, the findings are consistent with previous mathematical model predictions that shortening the interval between chemotherapy courses results in a more effective eradication of malignant cells and potentially improves survival. Also in this setting, the role of G-CSF is crucial to the success of therapy.

Non-Hodgkin's malignant lymphomas (NHL) are considered very sensitive tumors, and chemotherapy has the purpose of curing patients with aggressive disease. The most important toxicity of the employed regimens is myelosuppression, particularly in patients aged over 60 years, in advanced-stage disease and when the regimen is used as a salvage therapy. All of the studies that investigated the relationship between dose intensity and chemotherapy outcome suggest that dose reduction is detrimental to the response rate, time-to-treatment failure (TTF) and overall survival (OS). While increased dose intensity of CHOP or CHOP-like regimens by shortening the intervals between cycles improves OS, a planned or unplanned reduction in dose intensity of

these regimens given at standard intervals decreases clinical outcome. The prophylactic use of G-CSF is associated with the maintenance of planned dose intensity, which is not warranted after a neutropenic event. Finally, dose-dense chemotherapy supported by G-CSF always improves clinical outcome in terms of OS.

Ovarian cancer is a clinical example of high sensitivity to platinum compounds and taxanes. When these drugs are employed together with surgery, a cure with a low incidence of hematological toxicity is truly achievable. However, considering the median age of patients (sixth decade of life on average) and therapeutic setting of these drugs used as a palliative second-line treatment, the incidence and severity of neutropenia and febrile neutropenia increases. Under these clinical conditions, the employment of G-CSF according to international guidelines is strongly recommended.

In retrospective analyses, it has been shown that a reduction in dose intensity decreases the response rate, and an increased dose of the platinum compound does not improve OS. The use of G-CSF has not yet been investigated in prospective and randomized trials, and no available data exist on the increase of dose-dense chemotherapy in ovarian cancer.

The heterogeneous group of adult soft tissue sarcomas (STS) includes poor chemosensitive malignancies and highly responsive diseases, such as the Ewing family tumors. The most employed drugs are anthracyclines and oxaphosphorines with a dose intensity considered to be of great importance to clinical outcome, even though these drugs have demonstrated a significant bone marrow toxicity, particularly when employed in intensified regimens. Conclusive data have not yet been found on the usefulness of increasing or decreasing doses in STS, but increasing dose intensity has shown higher response rates in a metastatic setting and prolonged disease-free periods with adjuvant treatments of Ewing family tumors. Of note, the correct prophylactic employment of G-CSF is necessary to avoid severe hematological toxicities in standard treatments and allow dose-dense chemotherapy, chiefly in Ewing sarcomas with higher expected survival rates in patients with locally advanced disease. It seems that for this group of diseases, the more rational strategy of surgery, radiotherapy and chemotherapy can be of greater importance than the pursuit of high dose intensity chemotherapy.

In the past, small cell lung cancer was considered the paradigm of chemo- and radiosensitivity and defined as 'potentially curable'. However, published studies have shown an increase in response rate, and a small improvement in OS. Since the first employment of the platinum and etoposide combination, no new or more active drugs have been found. The only progress has been the combined chemo- and radiotherapy, which is able to prolong progression-free survival in limited disease, with a high rate of hematological and extra hematological toxicities that require the use of G-CSF. There is no evidence showing the role of dose intensity in the achievement of responses, however, a detrimental effect by dose reduction has been indirectly demonstrated, particularly in older patients and when the duration of responses is considered.

Germ cell tumors represent an exclusive model of curable solid tumors even in presence of advanced disease as the cells are very sensitive to antineoplastic agents, and the well-

established and profitable integration between chemotherapy and surgery. The role of dose intensity is well defined in obtaining a cure, and it is documented that a reduction of dose is detrimental and compromises the destiny of patients. In this scenario, the use of filgrastim and pegfilgrastim is mandatory and particularly important. Despite promising results, the trial of increasing dose-dense approach has not achieved the expected results, and future strategies for this disease are mainly focused on the recovery of relapsed patients and the employment of new drugs with biological targets.

In all the reviewed studies, the systematic use of G-CSF to prevent hematological toxicities and avoid a dose chemo-therapeutic change is highlighted. Hematological growth factors are prescribed to control severe neutropenia and reduce the risk of infective diseases in patients treated with myelotoxic chemotherapies. Filgrastim should be administered daily for up to 2 weeks until neutrophil count has reached 10,000/mm^3. In clinical trials, it has been demonstrated that the mean duration of G-CSF prophylaxis is up to 10-11 days. However, in daily clinical practice, many patients receive shorter courses of prophylaxis; and when G-CSF is employed for neutropenia treatment, the period of time is not well defined, but is usually up to the time of recovery from neutropenia. All of these clinical therapeutic approaches are not correct and certainly not compliant with the rules stated by international guidelines. A recent study examined the relationship between duration of prophylaxis and risk of hospitalization in patients receiving myelotoxic chemotherapy for NHL, breast cancer and lung cancer (107). The mean duration of filgrastim administration ranged from 4.3 days for lung cancer to 6.5 days for NHL. Of note, the multivariate analysis demonstrated a reduction in risk of hospitalization with each additional day of G-CSF administration. From this study and all studies on G-CSF prophylaxis, this strategy should be used for regimens in which the maintenance of dose intensity or increase of dose-dense is the most important tool for outcome. Whether the dose and duration of G-CSF administration are adequate, and pegfilgrastim plays an important role in this particular setting, the goal of maintaining dose intensity, improving the cure rate and avoiding hematological toxicities is easily achieved.

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