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REVIEW

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European School of Oncology European consensus on the use of granulocyte colony-stimulating factor: the example of breast cancer

Abstract An apparent chemotherapeutic dose-response relationship for patients with breast cancer has provided clinicians with the impetus to investigate further the usefulness of dose-intensification strategies in this setting. These approaches have provided promising results: noticeable improvements in response rates in terms of disease-free survival have been recorded, particularly when dose intensification has been used as first-line consolidation therapy for chemosensitive advanced disease and as consolidation in adjuvant therapy for high-risk patients. It may also be of use in the treatment of inflammatory and locally advanced disease. Although the results of prospective studies will help to define the potential advantages of dose-intensification strategies further, comparisons of myeloablative and subablative intensification regimens are needed to define the role of dose and dose intensity in this setting.

Key words Granulocyte growth factors · Breast cancer · Dose intensification · Peripheral blood stem cells

Introduction

Granulocyte growth factors (GGFs) have significant potential as supportive treatment in chemotherapy for malignant diseases. However, to date, standards for their rational use have not been established by the European medical community. On September 10, 1994, 70 leading European clinicians held a meeting in Munich under the auspices of the European School of Oncology (ESO) to develop a consensus on the most appropriate use and future development of GGFs. The workshop identified treatment of congenital agranulocytosis, enhancement of engraftment following bone marrow transplantation (BMT), use in engraftment failure, and support of high-dose chemotherapy as definite or acceptable indications for the use of GGFs. The use of growth factors in conventional solid-tumor management needs further assessment in large clinical trials to confirm reduced morbidity, decreased treatment-related costs, and improved quality of life. Primary prophylaxis is usually not appropriate, whereas secondary prophylaxis with GGFs should be considered in patients in whom maintenance of dose intensity is critical.

There was common recognition at the ESO meeting that one of the most important indications for growth factors is mobilization of peripheral blood progenitor cells (PBPC) for autotransfusion. Replacement of BMT by this technique was clearly seen as an imminent development. Recent treatment approaches such as high-dose chemotherapy or dose-intensification regimens require hematopoietic rescue with GGFs with or without PBPC transfusion. This represents another potentially important indication for this group of cytokines. However, the benefit of high-dose chemotherapy in terms of survival remains to be established for many tumors.

A good model for investigation of this new field is the treatment of breast cancer with high-dose chemotherapy and hematopoietic support. It has long been hypothesized that a dose-response relationship exists in the response of solid tumors to chemotherapy [27, 31, 55, 59]. Several preliminary studies have suggested that dose and dose intensity (dose per unit time) may be important factors in determining the response of patients with breast cancer to adjuvant therapy and treatment for metastatic disesase [9, 33, 37]. However, despite the increases achieved in the response rate, the use of 1.25- to 2-fold higher doses of chemotherapy (in the absence of hematopoietic support) has not generally led to significant increases in disease-free survival and/or overall survival (Table 1).

Recent well-designed studies suggest that a threshold dose may be an important determinant of morbidity and long-term survival [13, 63, 71]. The most conclusive

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Table 1 Dose-intensification studies in patients with MBC in whom hematological support was not used. (*CMF* Cyclophosphamide + methotrexate + fluorouracil, *ld* low-dose therapy, *hd* high-dose therapy, *CMFVP* cyclophosphamide + methotrexate + fluorouracil + vincristine + prednisolone, *CR* complete response, *FAC* fluorouracil + doxorubicin + cyclophosphamide, *FEC* fluorouracil + epirubicin + cyclophosphamide, *EP* epirubicin + prednisolone, *OR* overall response)

Study	Number of patients	Treatment		CR (% patients)	OR (% patients)	Median survival (months)
Beretta et al. [7]	103	CMF	ld	–	18	–
			hd		55	
Carmo-Pereira et al. [13]	48	Doxorubicin	ld	4	25	8
			hd	17	58	20
Forastiere et al. [26]	37	Cisplatin	ld	0	0	–
			hd	0	21	–
French Epirubicin Study Group [28]	259	FEC	ld	6	42	–
			hd	15	43	–
Habeshaw et al. [32]	209	EP	ld	4	23	11.5
			hd	10	41	11
Hoogstraten et al. [34]	283	CMFVP	ld	8	40	14
			hd	19	59	14
Hortobagyi et al. [35]	60	FAC	ld	22	78	20
			hd	25	78	20
Malik et al. [44]	30	FAC	ld	32	82	18
			hd	34	84	22
O'Bryan et al. [47]	68	Doxorubicin	ld	–	32	–
			hd	–	30	–
Tannock et al. [63]	113	CMF	ld	4	11	13
			hd	2	30	15.5

evidence for the existence of a dose-response relationship in the treatment of breast cancer comes from intensification studies in patients with advanced metastatic and/or refractory disease that have incorporated hematopoietic support, such as autologous BMT (ABMT) with or without hematopoietic growth factors and peripheral blood stem-cell (PBSC) transplantation [8, 17, 18, 22, 56, 62]. In these studies, doses of chemotherapeutic agents were increased 5- to 10-fold and were associated with an average overall response rate of 69% (range 44–80%). Furthermore, an average of 16% (range 6–25%) of patients achieved a complete remission (Table 2). Although the median duration of response was typically short, these studies suggested that dose intensification could overcome acquired or intrinsic resistance.

In addition to allowing dose intensification, the use of hematopoietic support may produce a significant reduction in morbidity and mortality due to chemotherapy-induced hematological toxicity. Moreover, the use of hematological support may allow dose-intensification regimens to be used as first-line therapy in the treatment of metastatic and high-risk breast cancer, including in patients with axillary node involvement or locally advanced and inflammatory disease.

Table 2 Dose intensification studies in refractory MBC in which all patients received hematological support

Study	Number of patients	CR (% patients)	OR (% patients)	Median response duration (months)
Bitran et al. [8]	19	11	74	3
Dunphy et al. [18]	24	13	67	6+
Dunphy et al. [19]	28	25	79	3–10
Eder et al. [22]	14	21	71	5
Slease et al. [57]	10	20	80	2–7
Tajima et al. [61]	16	6	44	4

Dose intensification in metastatic breast cancer

Results reported from initial studies showed that relapse occurred mainly at the site of the primary tumor and, particularly in the case of a large tumor mass, prior to intensification [2, 22, 40–42, 49, 51, 67, 70]. The results of these studies and other trials that reported the use of dose intensification in the treatment of hematological malignancies suggested that dose intensification should be used earlier in the evolution of the disease in chemosensitive patients, i.e., after tumor debulking.

Table 3 summarizes the results of published trials on the use of intensification regimens as consolidation of first-line induction chemotherapy in patients with metastatic breast cancer (MBC). Although the type of induction chemotherapy implemented before intensification varied considerably (thus making it difficult to make comparisons between studies) overall response rates of 59–100% were observed. Furthermore, complete responses were reported in 15–40% of patients.

Whereas most investigators used dose intensification for those patients who were considered to be chemosensitive after induction (i.e., a complete or partial response), some also proposed intensification in stabilized patients [5, 20, 24, 38, 39, 43, 57, 69]. Overall, dose intensification led to the conversion of partial to complete responses in an average of 29% (range 6–55%) of patients, whereas complete responses were observed in an average of 47% (range 34–73%) of patients, corroborating the hypothesis that a dose-response relationship exists in patients with MBC. Disappointingly, however, the duration of response (6–18 months) and the median duration of survival (12–24 months) did not differ significantly from the overall results obtained with conventional chemotherapeutic regimens.

Table 3 Dose intensification as consolidation in patients with MBC. (*CAF* Cyclophosphamide + doxorubicin + fluorouracil, *CAMF* cyclophosphamide + doxorubicin + methotrexate + fluorouracil, *CAMFV* cyclophosphamide + doxorubicin + methotrexate + fluorouracil + vincristine, *CSF* colony-stimulating factor, *CYC* cyclophosphamide, *FAM* fluorouracil + doxorubicin + mitomycin C, *GM-CSF* granulocyte-macrophage colony-stimulating factor, *AGMO* ABMT, *FACP* fluorouracil + cisplatin + doxorubicin + cyclophosphamide, *ICE* ifosfamide, carboplatin etoposide, *LOMAC* cyclophosphamide + doxorubicin + vincristine + methotrexate with leucovorin rescue, *OS* overall survival)

Study	Number of patients	Induction			Intensification				
		Protocol	CR (%)	OR (%)	Protocol	Hemato-logical support	CR (%)	OR (%)	OS at 24 months (%)
Antman et al. [1]	29	Not specified (?)	35	100	CYC Thiotepa Carboplatin	AGMO	48	100	>50
Ayash et al. [3]	20	Doxorubicin CYC	30	95	Melphalan CYC Thiotepa Carboplatin	PBSC+ CSF ABMT+ PBSC+G-CSF	35	90	–
Dunphy and Spitzer [17]	80	Doxorubicin CYC	30	74	CYC Etoposide Cisplatin	ABMT	55	79	33
Fields et al. [24]	49	Mini ICE various	37	71	Ifosfamide Etoposide Carboplatin	ABMT or PBSC ± CSF	41	–	45
Jones et al. [38]	45	FAM	38	91	CYC Cisplatin Carmustine	ABMT	64	100	–
Kennedy et al. [40]	30	CAMFV	27	80	CYC Thiotepa	ABMT, purged	46	100	50
Slease et al. [56]	15	CAMF-CAF	40	100	CYC Carmustine	ABMT	73	100	–
Williams et al. [69, 70]	59	LOMAC (n = 27)	15	71	CYC Thiotepa ± Carmustine	ABMT ± PBSC	34	51	20
		FCAP (n = 32)	25	59					
Baker et al. [5]	19	Not specified (?)	21	74	CYC Etoposide Carboplatin	ABMT ± CSF	42	84	–
Livingston et al. [43]	53	Not specified (?)	25	89	CYC Etoposide Cisplatin	GM-CSF	39	–	40
Vaughan et al. [65, 66]	26	Not specified (?)	19	100	CYC Thiotepa Hydroxyurea	ABMT ± PBSC GM-CSF	42	100	50

Comparative survival analysis

Considering the variations in the inclusion criteria of the studies summarized in Table 3 and that the MBC patients included in these trials represent less than 100% of all patients with metastatic disease, it is difficult to analyze the reported survival rates in comparison with historical studies of conventional chemotherapy. A metaanalysis of 5217 patients treated with conventional chemotherapy for MBC revealed a complete response rate of 8% (range 0–36%); the overall survival rates at 24 and 36 months were 39% and 25%, respectively [21]. Similarly, in a study of 1424 patients treated with the combination of fluorouracil, doxorubicin, and cyclophosphamide (FAC) as first-line chemotherapy for MBC, complete responses were achieved in 16% of patients, whose subsequent 5- and 10-year progression-free survival rates were 12.5% and 9%, respectively [36]. Since dose intensification achieves a complete response in 10–35% of patients with refractory disease [8, 17, 22, 42, 49, 56, 62, 67], i.e., similar to that achieved by conventional chemotherapy, it is unlikely that intensified regimens in their current form will lead to an improvement in disease-free or overall survival. The overall survival at 24 months following dose intensification ranges from 20% to 50% (Table 3).

When dose intensification is used to consolidate first-line induction chemotherapy, disease-free survival at 24 months appears to range between 20% and 30%, with the mean overall survival rate being 40–50%. At 3 years, 25–35% of patients remained alive and between 20% and 25% were disease-free. Interestingly, the subset of patients who achieve a complete remission prior to dose intensification obtain a genuine long-term benefit, with 40% achieving disease-free status and 45% remaining alive at 3 years [19, 30, 43, 49, 65, 66]. These promising results have prompted a number of prospective trials comparing conventional chemotherapy with dose-intensification protocols (such as cyclophosphamide, thiotepa, and carboplatin) in chemosensitive patients [6].

Table 4 Dose-intensification studies in breast cancer with massive axillary node involvement[a] (*DFS* Disease-free survival, *HD* high dose, *MTX* methotrexate, *RTE* radiotherapy)

Study	Number of patients	Treatment protocol		Locoregional therapy	DFS (%)	OS (%)
		Induction	Intensification			
Gianni et al. [29]	48	CYC (HD) Vincristine (HD) MTX (HD) Cisplatin	Melphalan	Surgery RTE	92 at 2 years	93 at 2 years
Overmoyer et al. [48]	32	Fluorouracil Doxorubicin CYC	Busulfan CYC Cisplatin Carmustine	–	85 at 3 years	89 at 3 years
Peters et al. [50]	85	Fluorouracil Doxorubicin CYC	Cisplatin CYC Carmustine	Mastectomy RTE	72 at 2.5 years	77 at 2.5 years
Schwartzberg et al. [54]	58	Fluorouracil Doxorubicin Mitomycin C	Thiotepa CYC Carboplatin	Surgery RTE	88 at 2 years	–
Tajima et al. [61]	36	–	CYC Doxorubicin Carmustine	Mastectomy	65 at 5 years[b]	78.5 at 5 years[b]
Van der Graaf et al. [64]	28	MTX Doxorubicin Vincristine Fluorouracil	CYC Etoposide Mitoxantrone Thiotepa	Surgery RTE	84 at 2 years	–

[a] Patients with involvement of >5 to 10 axillary nodes
[b] Patients with involvement of >10 axillary nodes (n = 18)

Dose intensification in high-risk patients

On the basis of the promising results obtained in MBC patients, a number of clinicians have proposed that dose intensification may be effective in the treatment of high-risk breast cancer. This includes patients with massive axillary node involvement and those with inflammatory or locally advanced disease.

Axillary node involvement

Breast cancer patients with >10 axillary nodes affected at the time of surgery unquestionably represent a high-risk population. Two large retrospective studies have shown that in the absence of adjuvant therapy, the percentage of relapse in the overall and disease-free survival of such patients at 5 and 10 years is <35% and 20–25%, respectively [25, 46]. However, the use of conventional adjuvant chemotherapy does not appear to have improved the prognosis of these high-risk patients [11, 12, 14, 25, 46, 52, 71]. For example, in a total of 1088 MBC patients with ≥11 nodes who received no chemotherapy, Nemoto et al. [46] reported that 22–29% of patients were disease-free at 5 years. Although the preliminary results of semiintensive (up to a 2.5-fold increase in dose) adjuvant chemotherapy regimens do not suggest that prognosis is significantly improved [11, 15, 71], several groups have tested the efficacy of dose intensification in high-risk breast cancer patients with axillary node involvement (Table 4). In these studies, 65–92% of patients were disease-free at 2–5 years following dose intensification. This compares favorably with the disease-free survival rate of 29–50% seen at 5 years after conventional adjuvant chemotherapy.

Although the results of the dose-intensification studies are encouraging, they are limited by the relatively short follow-up period. Therefore, further randomized studies are required to confirm the beneficial effects of dose intensification in such patients. However, given the finding that 20–40% of patients may achieve a complete response after conventional chemotherapy, it would appear prudent to define other prognostic and/or predictive factors that would allow better selection of patients likely to benefit from this strategy.

Inflammatory and/or locally advanced disease

There is little doubt that the integration of chemotherapy into a multimodality treatment strategy for inflammatory breast cancer (IBC) has led to a considerable improvement in the prognosis of this disease. The use of systemic chemotherapy has increased the survival rate at 5 years from <5% after locoregional treatment alone (i.e., surgery and radiotherapy) to >40–50%. However, 50–60% of these patients will nonetheless die as a result of metastatic disease [60].

It is now evident that the clinical and pathological responses (i.e., complete histological remission) to an induction regimen are the principal prognostic and/or predictive factors in patients with IBC [60]. Furthermore, these responses appear to be closely linked to the dose and dose intensity, suggesting a dose-dependent effect [16, 23, 45]. Since IBC is extremely chemosensitive, it appears to be a good candidate for dose intensification, and preliminary results have been very encouraging (Table 5). For example, in one study, 20% of patients with IBC achieved a complete histological remission, and the disease-free survival was 70% at 24 months [53]. Prospective studies are currently in

Table 5 Dose intensification studies in locally advanced and inflammatory breast cancer (*CHR* Complete histological remission, *DFS* disease-free survival, *OS* overall survival, *NA* not applicable, *hd* high dose, *RTE* locoregional radiotherapy

Study	Number of patients	Population	Induction regimen	Intensification	Loco-regional therapy	CHR (%)	Toxic death (%)	Median follow-up months (range)	DFS %	OS %
Willemse et al. [68]	21	IIIB	NA	Cyclophosphamide Etoposide	NA	15/20 (75)	1/20 (5)	36	71% at 36 months	80% at 36 months
Sledge et al. [58]	23	IIIB	FAC/CMF/ AC×5	Cyclophosphamide Carboplatin Etoposide	NA	NA	2/23 (7)	12 (0–26)	61% at 12 months	NA
Roché et al. [53]	20	Inflam-matory	FEC hd×4	Cisplatin Etoposide Cyclophosphamide	Surgery/ RTE	4/20 (20)	NA	26 (7–60)	70% at 24 months	80% at 24 months
Ayash et al. [4]	27	Inflam-matory IIIB	Doxorubicin hd×2	Cyclophosphamide Thiotepa Carboplatin	Surgery/ RTE	4/27 (15)	0	22 (5–38)	85% at 22 months	NA

progress to define further the potential advantages of dose intensification in patients with IBC.

For locally advanced breast cancer (stages IIIa and IIIb, excluding inflammatory forms) the situation is more complex and the results of dose-intensification studies are even more preliminary (Table 5). In this group of patients, it is clear that conventional systemic chemotherapy in combination with locoregional treatment has reduced the rate of metastasis and, in some studies, has led to an increase in disease-free survival. However, a significant benefit in terms of increased overall survival has yet to be demonstrated [10], although median follow-up periods have typically been short (10–36 months).

Conclusions

In patients with breast cancer, dose-intensification strategies have provided some encouraging results, particularly in the first-line consolidation of chemosensitive metastatic disease and as consolidation in adjuvant therapy of high-risk patients. Dose intensification may also be effective in the treatment of IBC and locally advanced breast cancer. The results of prospective studies, many of which are currently under way, will make it possible to define more clearly the potential advantages of this type of strategy. However, it is equally important that well-controlled trials also be initiated to compare myeloablative and subablative intensification protocols so as to define the exact roles of dose and dose intensity in such regimens.

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