



Joanna Zjawinska. *Sometimes His Expertise Had Annoyed Her*. Oil on canvas, 32" × 42".
Courtesy of the Hanson Gallery, New Orleans, Louisiana.

The role of chemotherapy intensification in breast cancer has not yet been fully clarified, but some aspects warrant additional investigation.

High-Dose Chemotherapy for Breast Cancer: The French PEGASE Experience

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Background: Early studies of high-dose chemotherapy (HDC) for breast cancer were limited by small numbers and the lack of adequate control groups. The French PEGASE Group was founded to perform larger and properly randomized comparative studies of this approach.

Methods: The program was created to determine the effects of intensive chemotherapy for breast cancer. The seven PEGASE protocols addressed HDC as adjuvant therapy (01 and 06) and as treatment for inflammatory nonmetastatic disease (02, 05, and 07) and metastatic disease (03 and 04). Two of these protocols are ongoing.

Results: The PEGASE 01 adjuvant therapy trial showed that 3-year disease-free survival was significantly better in the HDC arm but overall survival was unchanged. The ongoing phase III 06 trial is studying a higher dosage regimen. The HDC trials for metastatic and inflammatory nonmetastatic disease are encouraging.

Conclusions: Many clinicians no longer subscribe to the concept of HDC for breast cancer. Overall outcomes from management of poor-risk breast cancer remain poor; however, and it is possible that some selected subgroups of patients may benefit from such an approach.

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Introduction

In the early 1990s, tremendous enthusiasm developed for the application of intensive chemotherapy in treating breast cancer. Based on experience of high-dose chemotherapy (HDC) with hematologic diseases, HDC demonstrated some unexpected responses in patients with advanced breast cancer. Many small, open phase II studies were conducted first with alkylating agents alone, then with multidrug combinations

as salvage therapy for nonresponding metastatic patients, and finally for patients responding to conventional treatments.¹ An extension to the adjuvant setting was then initiated in nonrandomized trials.² A confusing debate within the oncology community and with patients' associations and insurance companies led to the organization of consensus conferences on efficacy and cost, as in Lyon in 1993.³ The requirement that phase III adjuvant studies must be large enough to detect survival differences in the magnitude of 10% to 20% was the basis for the formation of national and intergroup programs.

The French PEGASE Program

In 1994, the Fédération Nationale des Centres de Lutte Contre le Cancer and the Société Française de Greffe de Moëlle merged their clinical research activities on HDC for breast cancer into a national program. The High-Dose Chemotherapy for Breast Cancer Study Group (PEGASE) was formed to address strategic issues within large trials. With financial and logistic support from the Ligue Nationale Contre le Cancer, the Health Ministry, and some pharmaceutical companies, an independent clinical research unit was created in Paris. A steering committee was responsible for proposing specific trials in all clinical settings. Companion studies on prognostic and predictive factors, costs, and quality of life were conducted to examine all aspects of such an aggressive strategy. Four trials were accepted by the ethics committees, and the first patient was accrued in December 1994.

The first five studies, conducted between December 1994 and March 2000, selected 808 patients and entered 710 patients, 555 of whom were randomized into 36 active centers. This accrual represented 80% of all the women receiving HDC for breast cancer in France during this period (Table 1).

Adjuvant Trials: PEGASE 01 and 06

The PEGASE 01 protocol was designed to assess the value of one terminal high-dose regimen following conventional chemotherapy. The standard arm (arm A) used 4 cycles of FEC100 (500 mg/m² of fluorouracil, 100 mg/m² of epirubicin, and 500 mg/m² of cyclophosphamide every 3 weeks). The experimental arm (arm B) also received 1 cycle of CMA (120 mg/kg of cyclophosphamide, 45 mg/m² of mitoxantrone, and 140 mg/m² of melphalan [Alkeran]). Peripheral blood cell progenitors (PBCPs) were collected after the second FEC100 cycle. Granulocyte colony-stimulating fac-

Table 1. — PEGASE Group Trials (December 1994 to June 2000)

	Trial (reference)	Phase	No. of Patients	Status
Adjuvant	01 ⁴	randomized phase III	314	Closed 12/98
	06	randomized phase III		
Inflammatory	02 ⁸	phase II	100	Closed 9/96
	05 ¹⁰	phase II	55	Closed 6/99
	07	phase III		Ongoing
Metastatic	03 ¹¹	randomized phase III	180	Closed 6/00
	04 ¹²	randomized phase III	61	Closed 12/96

tor (G-CSF) was used to maintain the dose intensity after neutropenic episodes, to collect PBCPs, and to recover marrow after transplantation of 2.10⁶ CD34+/kg. Radiotherapy and tamoxifen were mandatory for hormone receptor-positive postmenopausal women. Inclusion criteria were age less than 60 years, more than 7 positive nodes, and no metastatic disease on a regular workup. The main statistical end point was an increase of 20% in disease-free survival at 3 years (β , 10%; α , 5%; unilateral test). Between December 1994 and December 1998, 314 patients entered the study. At a median of 39 months of follow-up, the first interim analysis was reported at the 2001 ASCO meeting.⁴ The main characteristics of the population were 68% premenopausal, 56% mastectomy, 30% negative estrogen receptors, and a median of 13 positive nodes. Tolerance was acceptable as only 1 patient died in arm B after intensification. No long-term toxicities have yet been registered. Of the 159 patients in arm B, 144 completed the treatment. Chemotherapy-induced amenorrhea occurred more frequently in arm B (80% vs 63%), but tamoxifen treatment was equally distributed in the two arms. At 3 years, disease-free survival (Fig 1) was sig-

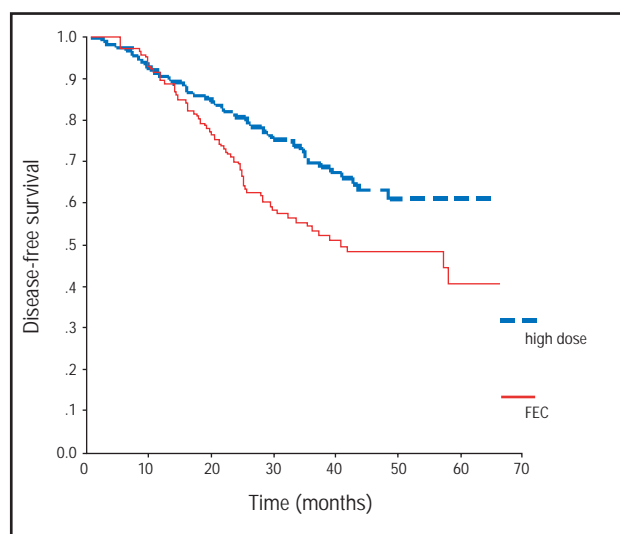


Fig 1. — Disease-free survival in the PEGASE 01 trial at a median follow-up of 36 months: 71% vs 55% ($P=.002$).

Table 2. — Outcome at 3 Years in the PEGASE 01 Trial

	Arm A (155 Patients)	Arm B (159 Patients)	Log Rank Test Significance
Disease-Free Survival	55%	71%	.002
Metastasis-Free Survival	60%	75%	.002
Event-Free Survival	53.5%	68.5%	.006
Median Survival With Metastasis	20 mos	10.7 mos	.2
Overall Survival	84%	85%	.33
Arm A = observation Arm B = intensification			

nificantly better in arm B (71% vs 55%, $P=.002$), as was event-free survival (68% vs 53%, $P=.006$). Overall survival, however, was equivalent since survival after progression was longer in arm A (20 vs 10.7 months) (Table 2). Using multivariate analysis, an advantage for arm B was significant only for disease-free survival (risk ratio 0.53 [0.39-0.74]). Estrogen-receptor positivity was the most powerful predictive factor for disease-free and overall survival, and vascular invasion was the most harmful factor for both end points. We are awaiting the results of the second analysis at 5 years, which should be available within the next few months.

Economic assessment showed an additional cost of 12,649 Euros (approximately \$13,000 US) for HDC, which was estimated to be 3.4-fold more expensive than standard-dose chemotherapy. The greatest component of the total cost was attributable to hospitalization time, with staff salaries accounting for most of this cost. Not

surprisingly, patients' self-assessment of quality of life demonstrated that HDC strongly deteriorates quality of life during treatment, with a decrease in all functional scale scores. Comparison of both arms revealed that physical functioning at the end of radiotherapy was significantly better for patients in the standard-therapy arm. Differences between arms disappeared 3 months after radiotherapy. However, 1 year after inclusion, when compared to patients in the standard-therapy arm, those in the HDC arm had physical and role functioning scores that were significantly lower and did not reach their baseline values. The delay to complete recovery will be assessed during the follow-up.

Our results are similar to those already available, with the studies designed in a similar way but in more favorable populations. Rodenhuis et al⁵ used the same induction treatment but a modified STAMP-V regimen for intensification. Bergh and colleagues⁶ compared a dose-dense, tailored FEC regimen to one terminal HDC regimen after conventional doses of FEC. The results favored the tailored FEC regimen arm in which the given dose intensity of epirubicin was the same as ours (Table 3). Longer follow-up is needed to determine the benefit of HDC. One shot of terminal HDC is capable of modifying the outcome of a nonmetastatic disease. High-dose-intensity programs without PBCP salvage should be considered and compared in well-designed trials.

We are conducting a new phase III trial (PEGASE 06) for the same population as in the 01 trial in which 6 cycles of FEC100 are compared to 4 sequential cycles of

Table 3. — Comparative Results in Three High-Dose Randomized Trials

	Trial					
	Bergh ⁶		Rodenhuis ⁵		PEGASE 01	
	9 t FEC	HD	5 FEC	HD	4 FEC	HD
Dose Intensity*						
Epirubicin (mg/m ² /week)	33	18	30	30	33	33
Cyclophosphamide (mg/m ² /week)	430	811	125	125	125	125
Cumulative Dose						
Epirubicin (mg/m ²)	780	181	450	360	400	400
Cyclophosphamide (g/m ²)	10.2	8.4	2.5	8	2	6.5
Intensification Regimen		Stamp-V		Stamp-V		CMA
3-Yr Disease-Free Survival	72%	63%	62%	77%	84%	85%
3-Yr Overall Survival	83%	77%	79%	89%	84%	85%
* Dose intensity according to Hryniuk W, Levine MN. Analysis of dose intensity for adjuvant chemotherapy trials in stage II breast cancer. <i>J Clin Oncol.</i> 1986;4:1162-1170.						
FEC = 5FU, epirubicin, cyclophosphamide						
CMA = cyclophosphamide, mitoxantrone, melphalan (Alkeran)						
HD = high dose						
9 t FEC = 9 cycles of tailored FEC						

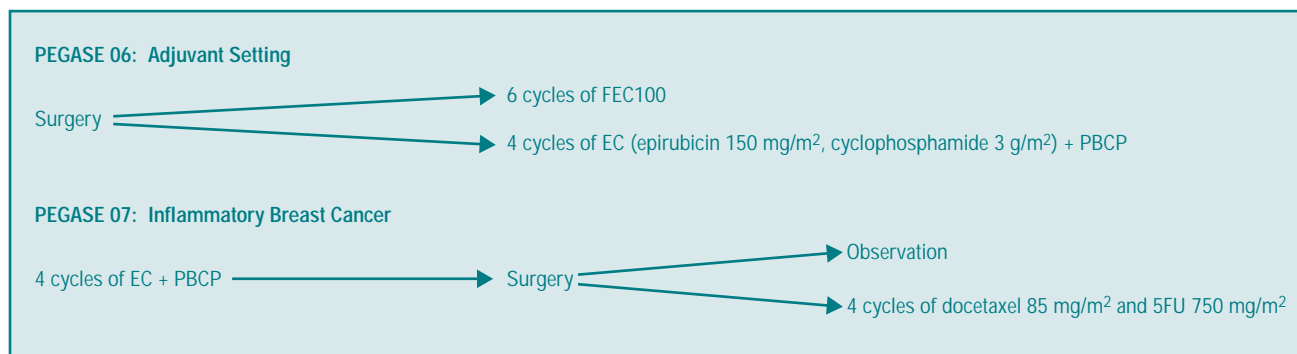


Fig 2. — Ongoing PEGASE protocols: 06 and 07.

HDC EC (150 mg/m² of epirubicin and 3 g/m² of cyclophosphamide every 3 weeks) with PBCP salvage (Fig 2).

Inflammatory Nonmetastatic Disease: PEGASE 02, 05, and 07

The first goal was to compare the pathologic complete response rate obtained by sequential HDC with historical series. The first phase II trial (PEGASE 02) delivered 4 cycles of cyclophosphamide (C), doxorubicin (D), and 5-fluorouracil (5FU) as follows:

- Cycle 1: C at 6 g/m², D at 75 mg/m²
- Cycle 2: C at 3 g/m², D at 75 mg/m²
- Cycles 3 + 4: C at 3 g/m², D at 75 mg/m², 5FU 2,500 mg/m² over 5 days

PBCPs were collected after cycle 1 and/or 2 and reinfused after cycles 3 and 4. G-CSF was administered throughout the 4 cycles. Mastectomy, radiotherapy, and tamoxifen (for estrogen receptor-positive patients) were planned after completion of chemotherapy.

Ninety-five patients were eligible and received 366 cycles of treatment. Eighty-seven completed the program, and relative dose-intensity was 0.97 and 0.96 for C and D. Febrile neutropenia was the most frequent toxicity, ranging from for 26% to 51% of cycles. Eighty-six patients underwent mastectomy for a median of 3.5 months.⁴⁻¹⁰ The pathologic complete response rate, defined as no infiltrating tumor cells in the breast, was 32% (±10%). The feasibility of such a procedure and the interesting response rate were therefore considered as encouraging.^{7,8} A specific survey on tolerance and cost confirmed the feasibility of sequential HDC.⁹

In a second phase II trial (PEGASE 05), we added 3 cycles of 100 mg/m² of docetaxel with G-CSF every 2 weeks after the first 2 courses of CD. Interim analysis led to the suspension of the study after 54 inclusions. Eight exhibited severe grade IV infections, and 2 deaths occurred during febrile neutropenia. Forty-

eight patients were assessable for response, and the pathologic complete response rate was 35%. We considered this regimen to be too toxic.¹⁰

In an ongoing phase III trial (PEGASE 07), after 4 cycles of EC (as in the 06 trial) with PBCP salvage and surgery, patients are randomized to either observation or 4 cycles of docetaxel at 85 mg/m² and 5FU at 3,000 mg/m² over 4 days (Fig 2).

Metastatic Disease: PEGASE 03 and 04

Two phase III trials were launched simultaneously in January 1995 for patients with metastatic breast cancer who were treated with first-line chemotherapy (Fig 3). Inclusion criteria were age less than 60 years, measurable or evaluable disease, and adjuvant cumulative dose of epirubicin or doxorubicin less than 450 and 300 mg/m², respectively. Median time to progression was the main statistical end-point in both studies.

In the PEGASE 03 trial,¹¹ patients with complete or partial responses were randomized after 4 cycles of FEC100 to receive no further treatment or 1 cycle of CHUT (800 mg/m² of thiotepa and 6,000 mg/m² of cyclophosphamide over 4 days). From 1995 to 2001, 308 patients were included. After a response had been validated in 180 patients, 91 were randomized to the standard arm without maintenance (arm A) and 89

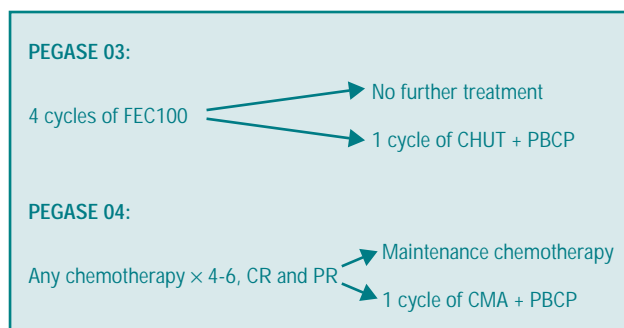


Fig 3. — PEGASE 03 and 04 profiles: phase III trials for metastatic patients treated with first-line chemotherapy.

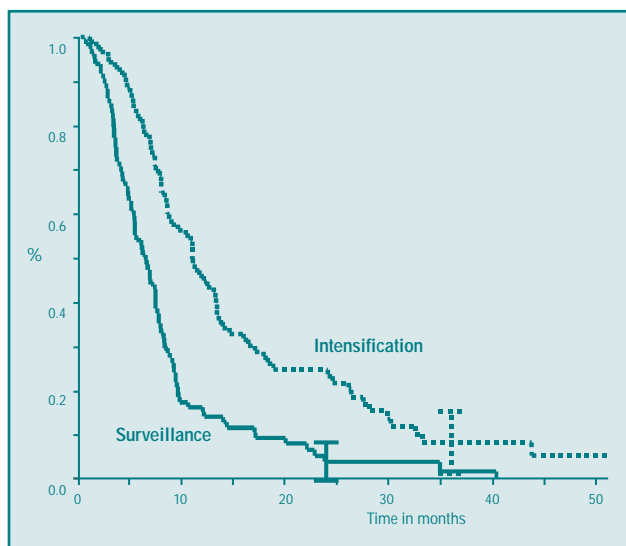


Fig 4. — PEGASE 03: progression-free survival.

were randomized to the intensified arm (arm B). The median age of the population was 46 years, 50% of the patients had bone metastases, 53% had liver involvement, and 59% were estrogen receptor-positive. Of the 89 selected patients, 80 received the CHUT regimen. One patient died of veno-occlusive disease. Three months after the last chemotherapy cycle, the response rate for arm A and arm B was 59% and 92%, respectively ($P=.01$), and the 1-year progression rate for 80% for arm A and 54% for arm B ($P=.0005$). The 1-year disease-free survival rate was 19% and 46%, respectively ($P=.0001$). Overall survival was not statistically different at 3 years (30% for arm A vs 38% for arm B) (Fig 4).

In the PEGASE 04 trial,¹² responding patients received 4 to 6 cycles of combination chemotherapy and then were randomized to maintenance chemotherapy or to 1 cycle of CMA (as in the 01 trial). Due to insufficient accrual, this trial was suspended after 61 patients were enrolled, 29 in the maintenance arm (arm A) and 32 in the CMA arm (arm B). The median age of the population was 44 years, 64% had received adjuvant anthracycline, and 20% had only one involved site. Of the 32 patients in arm B, 28 received HDC. Seven exhibited a grade III-IV infection, and 3 patients converted from partial to complete response. At a median of 52 months of follow-up, all of the criteria favored arm B over arm A: median time to progression (17 vs 6 months), disease progression at 3 years (72% vs 96%), median survival (44 vs 18 months), and 3-year overall survival (61% vs 28%). Metastasis at only one site and no liver involvement were significant favorable prognostic factors.

Other phase III trials (Canadian¹³ and Anglo-Celtic¹⁴) with the same schedule demonstrated the same profile of early benefit on PFS. However, they

failed to demonstrate a longer overall survival after HDC, possibly due to a short follow-up and underpowered accrual.

Conclusions

The concept of high-dose chemotherapy for breast cancer has been diminished programs that were too small, by manipulated results from an isolated investigator, and by the lack of large differences in the first trials. Consequently, accrual in ongoing, well-designed studies is dramatically decreasing. However, the limitations of the high-dose strategy have not yet been clearly established, and future results may reverse the general opinion. Better selection of patients and relevant biological predictors may identify subgroups of patients who would benefit from the dose-response theory. Until new agents that improve the outcome of poor-prognosis breast cancer are developed, we, as others, will continue to explore the role of HDC.

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