High-dose chemotherapy for breast cancer and germ cell tumours in Europe

Wysokodawkowa chemioterapia w raku piersi i guzach zarodkowych w Europie

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ABSTRACT

High-dose chemotherapy for breast carcinoma as well as for germ cell tumours and many other adult solid tumours is becoming a diffuse treatment option in many European centres, despite very few controlled data existing on its role. Mortality rate has constantly declined in the last few years, probably due to the introduction of peripheral blood progenitor cells and haematopoietic growth factors, but also to a better patients' selection. In this paper we outline the European activity, with specific interest on the major ongoing randomised trials in breast cancer and germ cell tumours.

KEY WORDS: *high-dose chemotherapy in breast cancer and germ cell tumours, randomised European trials*

STRESZCZENIE

Wysokodawkowa chemioterapia w raku piersi a także w guzach zarodkowych i innych guzach litych u osób dorosłych staje się coraz szerzej uwzględnianym sposobem leczenia w wielu krajach Europy, mimo że istnieje znikoma liczba kontrolowanych badań dotyczących tego problemu. Śmiertelność związana z wysokodawkowaną chemioterapią bardzo wyraźnie spadła w ciągu kilku ostatnich lat, prawdopodobnie w wyniku wprowadzenia leczenia wspomagającego z uwzględnieniem komórek macierzystych z krwi obwodowej i homeopatycznych czynników wzrostu, a także lepszej selekcji pacjentów do tego typu badań. W pracy przedstawiamy aktywność europejskich ośrodków ze szczególnym uwzględnieniem randomizowanych badań w raku piersi i guzach zarodkowych.

SŁOWA KLUCZOWE: *wysokodawkowana chemioterapia w raku piersi i guzach zarodkowych, badania randomizowane w Europie*

INTRODUCTION

In the last ten years high-dose chemotherapy with haematopoietic rescue has been largely employed both in Europe (11) and in North America (2) for the treatment of haematological malignancies and solid tumours. In Europe alone more than 16 000 patients received allogeneic or autologous bone marrow or peripheral blood progenitor cells transplantation in 1997, but the vast majority of patients underwent an autologous transplant. The leading disease in Europe for high-dose chemotherapy and haematopoietic rescue is non-Hodgkin lymphoma with nearly 3000 patients, followed by breast carcinoma (2600 patients in 1997), while in the USA (1) breast cancer overtook non-Hodgkin lymphoma three years ago. The most important facts happening in the field of high-dose chemotherapy were the reduction of mortality which was as high as 15-18% at the turn of the decade and the shift from autologous bone marrow transplantation to peripheral blood progenitor cells (PBPC) reinfusion. Figure 1 shows the reduction in toxic death rate in Europe (European Group for Blood and Marrow Transplantation Database) in the last decade for solid tumours. With the advent of PBPC and haematopoietic growth factors the duration of hypoplasia

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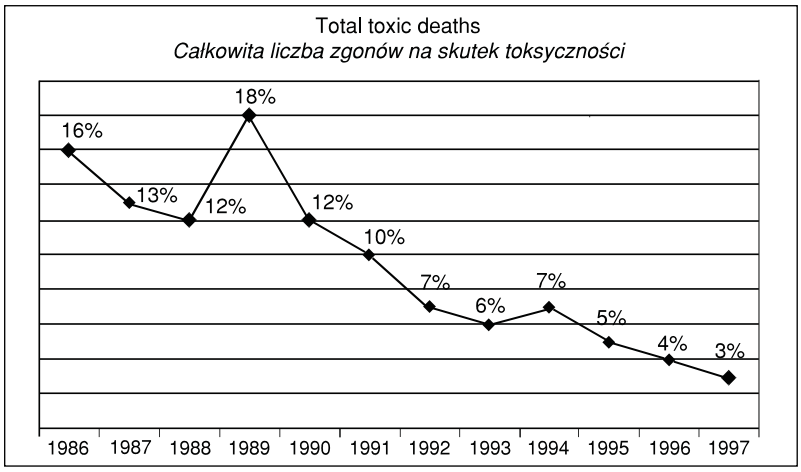

FIGURE 1. **Toxic related death rate (before 100 days from transplantation) for solid tumours in Europe during the years. (EBMT database)**

RYCINA 1. **Śmiertelność związana z toksycznością (wcześniej niż 100 dni od transplantacji) dla guzów litych w Europie w kolejnych latach (baza danych EBMT)**

has been reduced to 5-9 days as for granulocytes as well as for platelets, so leading to a reduction of time spent in hospital and costs of the entire procedure.

BREAST CARCINOMA

As mentioned earlier, breast carcinoma is facing a dramatic increase in terms of total number of procedures, Spain being the country with the highest number of transplants (more than 700 in 1997 alone) performed. If one argues which are the reasons why such an expensive, high-tech procedure is so diffuse, there might be several reasons: from the pessimistic point of view no many breakthroughs happened in the field of solid tumour treatment in the last two decades, while from the optimistic side excellent results have been published in the early '90s concerning the efficacy of high-dose chemotherapy in advanced breast carcinoma with complete responses in the range of 40 to 70% with a percentage of patients reaching a disease free status plateau at 3 years of 15 to 25% (1). Adjuvant high-dose treatment was employed only recently (1), probably due to the risk of employing such a toxic treatment to a good-risk population, compared to the one with overt metastatic disease. Mortality rate in the EBMT data base for all 800 patients treated with this modality is in the range of 1% (7) which is not too far from what is generally observed with major standard-dose chemotherapy regimens.

As regards metastatic disease we are still far from a consensus on the role of high-dose chemotherapy, and only one randomised study exists coming from Johannesburg (3) (see the chapter by Bezwoda in this issue) as well as on the preferable schedule. In Europe STAMP V program (Carboplatin 800-1600 mg/sqm, Cyclophosphamide 6.4 g/sqm and Thiotepa 500 mg/sqm) is largely employed. The best results in advanced breast cancer have been observed when patients are intensified in Complete Remission (2); the EBMT data base confirm these data (fig. 2 shows the event free survival of patients grafted in CR versus those patients intensified in other phases of their disease-EBMT database). There has been a recent enthusiastic interest in the field of high-dose chemotherapy for high-risk operable breast carcinoma after the publication of exciting results from Europe (8) and from the USA (10). The EBMT registry has collected more than 600 patients treated with high-dose chemotherapy: from this wide series again it seems that the results might be better than those achieved with standard-dose schedules (fig. 3). In a little cohort of patients with bad prognostic features (>20 positive axillary nodes involved) the results are very promising (fig. 4).

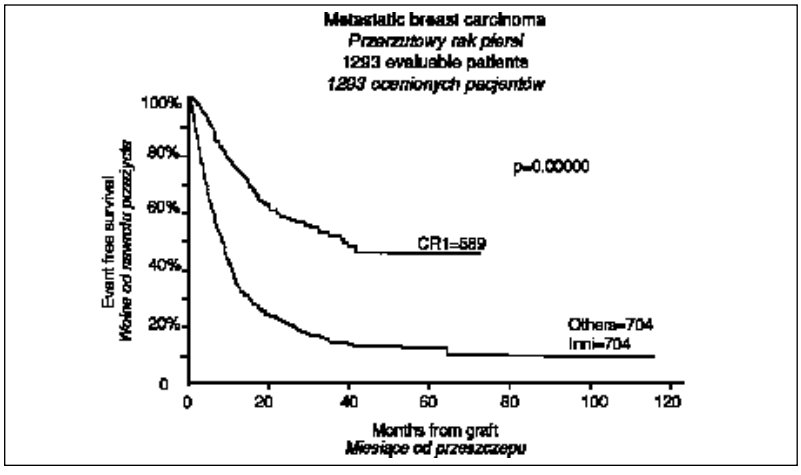

FIGURE 2. **Metastatic breast cancer: improved results by CR status at transplantation (EBMT Database)**

RYCINA 2. **Przerzutowy rak piersi: lepsze wyniki w całkowitej remisji przy transplantacji (baza danych EBMT)**

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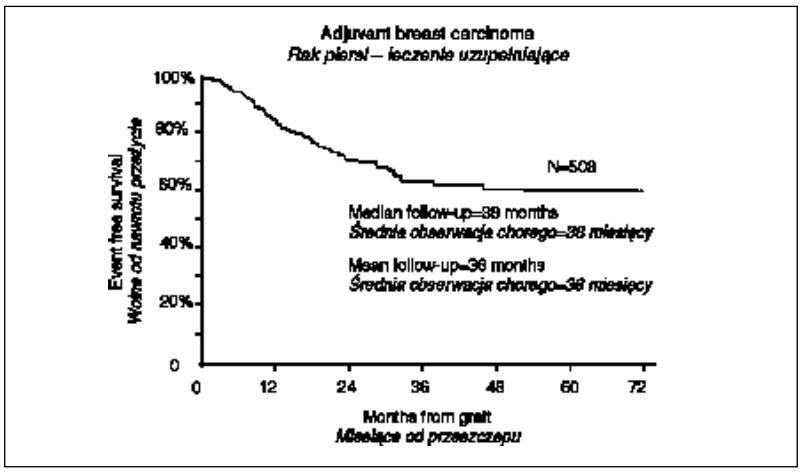

FIGURE 3. **Event-free survival for high-risk operable breast carcinoma. (EBMT database)**
RYCINA 3. **Wolne od nawrotu przeżycie w operacyjnym raku piersi przy wysokim ryzyku (baza danych EBMT)**

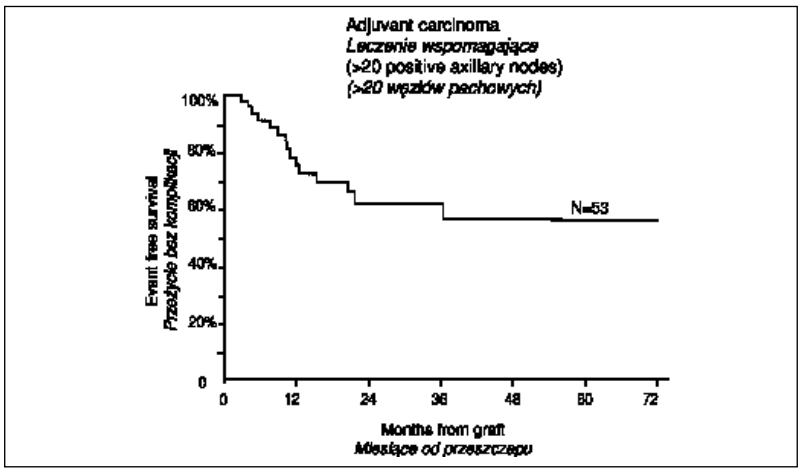

FIGURE 4. **Event-free survival for high-risk operable breast carcinoma with >20 axillary nodes. (EBMT database)**
RYCINA 4. **Wolne od nawrotu przeżycie w raku piersi przy wysokim ryzyku >20 węzłów chłon-nych (baza danych EBMT)**

ONGOING EUROPEAN STUDIES IN BREAST CANCER

Metastatic disease

One of the early studies to be activated by the French Federation of Centres for the Fight against Cancer (FNCLCC) was PEGASE 03 (from 1996 became a joint PEGASE/EBMT Study). In this trial metastatic patients not previously treated for advanced disease receive FEC (Epirubicin 100 mg/sqm) or FEC followed by cyclophosphamide 6 gr/sqm, mitoxantrone 45 mg/sqm and alkeran 140 mg/sqm. This study will probably be closed in Autumn 1998 with 300 patients. The trial that will probably be the major one in the near future is the so-called EBDIS 1 (European Breast Dose Intensity Study 1), which recently became also an EBMT study and joint accrual started in March 1998. In EBDIS1 patients with untreated metastatic disease are randomised between a standard arm consisting of docetaxel 75 mg/sqm and adriamycin 50 mg/sqm for 4 courses followed by 6 courses of classic CMF. The experimental arm consists of 3 docetaxel/adriamycin courses followed by a tandem high-dose chemotherapy of VIC (known also as ICE) – ifosfamide 12 g/sqm, carboplatin AUC 18, and etoposide 1200 mg/sqm, followed by high-doses of cyclophosphamide (6 g/sqm) and thiotepa (800 mg/sqm). From the first commitments by many centres, it seems that the 400 patients accrual goal will be possibly achieved in two years. So far all the phase II studies, as well as PEGASE 3, evaluated the role of high-dose chemotherapy considered as a single-shot treatment. High-dose sequential chemotherapy, i.e. the rapid recycling of various active drugs, at maximum doses, in order to reduce the onset of drug resistance, is under evaluation in naive metastatic patients. In this trial chaired by our group, cyclophosphamide is delivered at 7 g/sqm, followed after two weeks by vincristine 2 mg and methotrexate 8 g/sqm and a week after epirubicin is delivered at 150 mg/sqm with PBPBC harvesting. Another course of epirubicine is then delivered, followed by cisplatin 100 mg/sqm and etoposide 360 mg/sqm in three days; the last segment is the real high-dose one with thiotepa 500 mg/sqm and alkeran 140 mg/sqm followed by PBPCT and filgrastim. G-CSF is also administered after cyclophosphamide and epirubicin in order to deliver drugs on time. Thirty-six patients have been enrolled so far, and toxic death rate was 0%. Total number of days spent in hospital for the entire program is in the range of three weeks.

Adjuvant studies

At least a dozen major phase III randomised studies are ongoing throughout Europe with the following characte-

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ristics: 1) reduced number of positive axillary nodes as an entry criterion compared with the North American rules. The most recent trials enroll patients with >3 positive nodes whereas in the USA the required number was until last year >9; 2) the maximum age for entry is increasing up to 60 years, resulting in a larger population suitable for these investigations; 3) the "oldest" or "first generation" studies employ the single high-dose shot as intensification treatment after 4 to 6 standard courses (e.g. FEC), while the "second generation" ones apply new concepts such as high-dose sequential chemotherapy. Table I shows the major European ongoing adjuvant studies in high-risk breast cancer (updated June 1998).

TABLE I. **Major ongoing European phase III adjuvant randomised studies**
TABELA I. **Główne europejskie aktualne badania losowe fazy III w leczeniu uzupełniającym**

Major european ongoing adjuvant studies in breast cancer (June 1998)
Główne europejskie aktualne badania w uzupełniającym leczeniu raka piersi (czerwiec 1998)

Group *Grupa*	#nodes *liczba węzłów*	Standard *Standard*	High-dose *Wysoka dawka*	#pts *Liczba pacjentów*	Mobilizing *Mobilizacja*
Italian *Włoska*	≥4	EPI→CMF	HDS	375	EPI 120 mg/sqm
Anglo-Celtic *Anglo-celtycka*	≥4	ADM→CMF	ADM+CT	446	CTX 4 g/sqm
Scandinavian *Skandynawska*	≥5 or >8	FEC	FEC+STAMP V	500	FEC
Netherlands *Holenderska*	≥4	FEC	FEC+STAMP V	720	FEC
EBMT/PEGASE	≥8	FEC	FEC+CMA	286	FEC
German *Niemiecka*	≥10	EC→CMF	EC→CMT	197	FEC
IBCSG 15-95	≥4	EC→CMF	HD-EC	199	Filgrastim

HDS – high-dose sequential Carboplatin
Karboplatyna wysokodawkowa sekwencyjna
CMA – Cyclophosphamide, Mitoxantrone, Alkeran
Cyclofosfamid, Mitoksantron, Alkeran
CMT – Cyclophosphamide, Mitoxantrone, Thiotepa
Cyclofosfamid, Mitoksantron, Tiotepa
HD-EC – High-dose Epirubicin/Cyclophosphamide
Epirubicin/Cyklofosfamid wysokodawkowe
STAMP V – Cyclophosphamide, Thiotepa, Carboplatin
Cyklofosfamid, Tiotepa, Karboplatyna

Germ cell tumours

The results of the treatment of metastatic testicular germ cell tumours have been dramatically improved by cisplatin-containing chemotherapy regimens: being BEP (Bleomycin, etoposide and cisplatin) and the surgical removal of residual masses, the gold standard of treatment (4).

Investigators at the Gustave Roussy Institut studied a cisplatin-based chemotherapy dose regimen as consolidation treatment for patients with poor-risk disease (6) in 28 patients who received two cycles of the PVeBV regimen followed by high-dose chemotherapy, with a NED rate of 43%. The subsequent randomised study compared this regimen to 4 cycles of PVeBV. The results (5) failed to demonstrate any survival advantage for high-dose chemotherapy, so new strategies have to be tested for bad prognosis germ cell cancers upfront. At the present time the best indication seems to be the one of late intensification in patients with "sensitive relapse", indicating those patients with a relapse after complete remission, but still responding to a platinum containing regimen. From the EBMT data base (fig. 5) very interesting results have been achieved in this subset.

Nevertheless, as in all other solid tumours, high-dose chemotherapy should be proposed to germ cell tumours patients only in clinical trials in order to avoid waste of time and to come to a final response as for the patients as well as for the scientific community. In order to finally clarify the role of high-dose chemotherapy in this peculiar disease, the EMBT launched a phase III randomised study in 1994, known as IT-94. It compares a standard arm (four courses of standard-dose containing chemotherapy) with an experimental arm where three courses of the same standard dose schedule are followed by a single-shot intensification with CARBOPEC (Carboplatin at different doses depending on the creatinine clearance, with a maximum of 2200 mg/sqm, etoposide 1200 mg/sqm, and cyclophosphamide 6.4 g/sqm). Patients in incomplete remission after first-line chemotherapy and those relapsing after previous CR are candidates for IT-94. In June 1998 190 has been entered from 11 countries.

CONCLUSIONS

When facing with high-dose chemotherapy in breast carcinoma and in germ cell cancer, one should keep in mind that in 1998 no one solid tumour should be conside-

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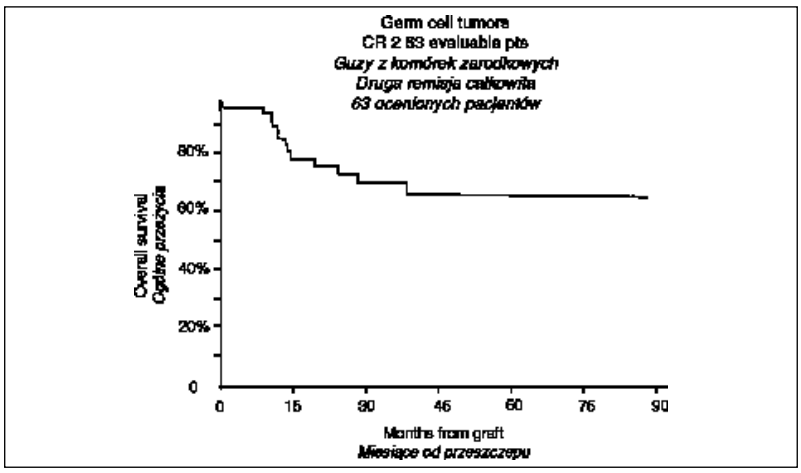

FIGURE 5. **Survival for germ cell tumour patients in sensitive relapse at the time of transplantation (EBMT database)**

RYCINA 5. **Przeżycie pacjentów z guzami z komórek zarodkowych przy wrażliwym nawrocie choroby w momencie transplantacji (baza danych EBMT)**

red as a candidate for this experimental treatment modality outside a clinical trial and all efforts should be made to enroll patients in prospective trials (9).

The next couple of years should be entirely devoted to complete the several ongoing studies, and to address specific questions like the role of contamination of PBPC and to define new strategies to reduce the costs as for example to start pilot European studies of outpatients high-dose chemotherapy programs. But to avoid uncontrolled proliferation of new small centers with inadequate experience in this fascinating but difficult field, a serious program of accreditation on a national or preferably European basis is going to be launched by the EBMT in the very near future.

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