

* CHAPTER 31

HSCT for solid tumours in adults

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1. Introduction

In the years 2005–2007, 3631 autologous and 192 allogeneic transplants for solid tumours in adults were reported to the EBMT. Most transplants (3596) were performed with PBPC, a small minority (215) with BM cells, and 7 with cord blood. Diseases treated by transplant can be roughly categorised as: sarcoma and primitive neuroectodermal tumour (pNET) (891), central nervous system (CNS) tumours, including neuroblastoma (1041), germ cell tumours (934), epithelial tumours (624). These numbers are probably an underestimate because not all transplants are currently registered with the EBMT. However, some general conclusions can be drawn:

1. Compared with previous years, the number of transplants is:
 - increasing for sarcoma/pNET;
 - stable for CNS and germ cell tumours;
 - decreasing for epithelial tumours.
2. The existence of a dose-response effect in epithelial tumours (breast, ovarian, small cell lung cancer) is still a matter of investigation. The benefit of autologous transplant in breast cancer has not been confirmed by randomised studies; however, an appreciable number of transplants is still being performed for breast cancer (206 in 2005, 116 in 2006). At the 2007 San Antonio Breast Cancer Symposium, the results of the EBMT-MD Anderson meta-analysis on 15 randomised phase III trials comparing high-dose with conventional-dose chemotherapy have been reported (1). These results, while not supporting a survival advantage for high-dose chemotherapy (HDCT), suggest that selected subsets of patients may profit from HDCT. In 2007 the report was published by AGO-OVAR/AIO and EBMT of the randomised phase III study for first-line treatment of advanced ovarian cancer in which high-dose sequential chemotherapy with peripheral blood stem cell support was compared with standard dose chemotherapy (2). No statistically significant difference in progression-free survival or OS was observed, and the authors concluded that HDCT does not appear to be superior to conventional dose chemotherapy. Small-cell lung cancer is the third epithelial tumour for which a phase III trial has been organised by EBMT. The results of this randomised study will be published shortly (3).
3. Allografting for solid tumours decreased in the period 2005–2007, for all indications. The transplant-related mortality attributable to the conditioning regimen and to GvHD (around 10% in most studies) makes it difficult to offer allografting as a salvage treatment to patients with metastatic disease and poor prognosis. Attempts to improve the therapeutic index of allogeneic transplantation in solid tumours by innovative clinical strategies are underway.

In order to highlight changes in the clinical indications for transplant in solid tumours in adult population, we will concentrate on three issues: germ cell tumours, breast cancer, and allogeneic transplant.

2. Indications for transplant

2.1. Germ cell tumours

In 2006, autologous transplantation for germ cell tumours was considered a standard therapy for sensitive relapse, and a clinical option for refractory disease, according to the EBMT indications (4). An authoritative confirmation of these guidelines came in 2007 from the publication of Einhorn et al. in the *New England Journal of Medicine* (5). They conducted a retrospective review of 184 consecutive patients with metastatic testicular cancer who had progressed after receiving cisplatin-containing combination chemotherapy. One hundred seventy-three patients received two consecutive courses of HDCT consisting of 700 mg of carboplatin/m² and 750 mg of etoposide/m² each for 3 consecutive days, and each course followed by an infusion of autologous peripheral-blood haematopoietic stem cells; the other 11 patients received a single course of this treatment. Of the 184 patients, 116 had complete remission of disease without relapse during a median follow-up of 48 months (range, 14 to 118). Of the 135 patients who received the treatment as second-line therapy, 94 were disease-free during follow-up; 22 of 49 patients who received treatment as third-line or later therapy were disease-free. Of 40 patients with cancer that was refractory to standard-dose platinum, 18 were disease-free. A total of 98 of 144 patients who had platinum-sensitive disease were disease-free, and 26 of 35 patients with seminoma and 90 of 149 patients with non-seminomatous germ-cell tumours were disease-free. It is clear from these data that testicular tumours are potentially curable by means of HDCT and haematopoietic stem-cell rescue, even when this regimen is used as third-line or later therapy or in patients with platinum-refractory disease.

The role of HDCT as first-line treatment in patients with metastatic germ cell tumour (GCT) and poor-prognostic clinical features was investigated by Motzer et al. (6). They randomised 219 previously untreated patients with intermediate- or poor-risk GCT to either four cycles of standard bleomycin, etoposide and cisplatin (BEP alone), or two cycles of BEP followed by two cycles of HDCT containing carboplatin and autologous transplant. The 1-year durable complete response rate was 52% after BEP-HDCT and 48% after BEP alone ($p=0.53$), leading to the conclusion that the routine inclusion of HDCT in first-line treatment for GCT patients with metastases and a poor predicted outcome to chemotherapy did not improve treatment outcome.

2.2. Breast cancer

According to the 2006 EBMT indications, autologous transplantation for breast cancer in the adjuvant and responding metastatic setting is in a developmental phase. The role of adjuvant HDCT with autologous transplantation for primary breast cancer at high risk of recurrence (at least 4 involved axillary lymph nodes) remains ill-defined. Data from individual trials have limited power to show overall or subgroup benefit for this indication. For this reason, the MD Anderson Cancer Center and the EBMT STWP set up a single database of individual patient data from 15 known randomised trials of HDCT vs. standard-dose chemotherapy (SDCT). Disease-free survival (DFS), breast cancer-specific survival (BCSS), and overall survival (OS) were the endpoints of the analysis. Subgroup analyses were by age, hormone receptors (HmR) and menopausal (MP) status. Median follow-up for 6,210 patients (3,118 HDC, 3,092 SDC) was 6 years (range, 0–15.3). Data were presented at the 2007 SABCS meeting, and will be presented at the 2008 EBMT meeting. After adjusting for age, trial and MP status, HDCT was found to prolong DFS, but not BCSS or OS. After adjusting for HmR in the subset for which that information was available, HDC was found to prolong DFS and had modest but significant benefits on BCSS and OS (HR 0.89; 95%CI 0.81–0.98; $p=0.016$) compared to SDC. In conclusion, HDCT as used in these 15 randomised studies prolongs DFS when used as adjuvant therapy in breast cancer. HDCT has at most a modest benefit on BCSS and OS compared to SDC. Whether HDCT has benefit in the context of contemporary taxane-based regimens and targeted therapies is unknown and may be resolved by future clinical trials.

2.3. Allogeneic transplant

Allografting is considered a developmental therapy for renal, breast and ovarian cancer, and not recommended for all other solid tumours. Allogeneic HSCT for solid tumours have been registered in the EBMT database, since 1995. The numbers of allogeneic transplants increased to 194 in 2002, concurrently with the publication of favourable reports and the implementation of an EBMT cooperative phase I study of allografting in solid tumours. Subsequently, a steady decrease in the annual numbers of transplants has occurred. [Table 1](#) shows the numbers of allogeneic transplantations registered at EBMT in the period 2005–2007. Reasons for the recent decrease have been:

- the introduction in clinical trials of molecularly targeted agents, especially for renal cancer,
- the lack of well designed phase II studies,
- the high rate of transplant-related mortality due to accrual of rapidly progressing, high tumour burden patients.

Table 1: Allogeneic transplants for solid tumours, 2005-2007 (data reported to the EBMT)

Tumour type	Number
Osteosarcoma	5
PNET	1
Ewing sarcoma	6
Medulloblastoma	5
Neuroblastoma	44
Ewing sarcoma/PNET, skeletal	1
Germ cell tumours	4
Ovarian carcinoma	8
Melanoma	4
Langerhans cell histiocytosis	4
Small cell lung cancer (SCLC)	1
Soft tissue sarcoma	2
Rhabdomyiosarcoma	22
Synovial sarcoma	3
Breast carcinoma	22
Undifferentiated carcinoma	2
Thymoma	1
Gastric carcinoma	1
Metastatic, unknown origin	1
Wilms tumour	3
Renal cell carcinoma	35
Other	17
TOTAL	192

A considerable amount of clinical data has been accumulated in several tumours, particularly in RCC (335 transplants), breast cancer (143 transplants), neuroblastoma (70 transplants), Ewing's sarcoma (39), ovarian carcinoma (40), colon carcinoma (39), and other entities.

The identification of the major mechanisms of neoplastic transformation has introduced into the clinic a series of innovative drugs that inhibit the molecular targets relevant to tumour phenotype. Many of these compounds have already been

approved for diseases that are targets of allogeneic transplantation (e.g., renal cancer, breast cancer, colorectal cancer). Major advances have been made in advanced renal cancer, in which the inhibition of the EGF/RAS/RAF/MAP kinase pathway has resulted in the doubling of progression-free survival in previously treated patients (7), and blockade of AKT/PI3K/mTOR pathway has resulted in a survival advantage in patients with poor prognostic factors (8). Inhibition of VEGF or VEGF-initiated signalling by bevacizumab or by sunitinib has also demonstrated considerable anti-tumour activity (9, 10). Targeted therapy has distinct advantages over a complex treatment such as allogeneic transplantation: It can be conveniently administered on an outpatient basis, it can be withheld if side effects occur, it does not require the supportive care needed for allogeneic transplantation. Indeed, patient referral for allogeneic transplantation has considerably decreased over the last two years, following the introduction in clinical trials of these drugs. However, targeted therapy is not devoid of side effects, it is not active in a considerable fraction of patients, and, most importantly, complete responses occur rarely, if not at all. In spite of its relevant associated mortality, allogeneic transplantation has the potential of inducing complete responses, some of which are long-lasting.

3. Concluding remarks

Relapsed germ cell tumours remain an indication for HDCT with autologous transplantation; poor-risk disease does not seem to benefit from HDCT upfront. Adjuvant breast cancer should be the focus of further randomised investigation, considering that all published studies have not included new drugs (e.g., taxanes, HER2/neu inhibitors) in the treatment program. At this stage, allogeneic transplantation should only be considered in patients without conventional therapeutic options. Further research is needed to translate the graft versus tumour effect into meaningful clinical benefit. Experimental and preliminary clinical data indicate that targeted therapies may powerfully complement the immune effect of allogeneic transplantation, rather than replace it.

References

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Mutiple Choice Questionnaire

To find the correct answer, go to <http://www.esh.org/ebmt-handbook2008answers.htm>

1. Autografting is indicated as adjuvant therapy in breast cancer:

- a) Only with positive hormone receptors
- b) Only in patients below 65-yrs old
- c) In patients with BRCA-1/2 positive tumours
- d) None of the above

2. High-dose chemotherapy with autologous transplantation in ovarian cancer:

- a) Has been utilised only in phase II trials
- b) Has undergone phase III trials of comparison with standard-dose chemotherapy
- c) Has proven useful in suboptimally debulked patients
- d) Is the treatment of choice for optimally debulked patients

3. Relapsed non-seminomatous germ-cell tumours may benefit from high-dose chemotherapy:

- a) Only in first relapse
- b) Only as consolidation of remission
- c) After first or subsequent relapses
- d) Only when the disease is platinum-refractory

4. Transplant-related mortality of allografting in solid tumours is:

- a) Below 1%
- b) Approximately 10%
- c) Between 2 and 4%
- d) Above 20%

5. Allogeneic transplantation for solid tumours has been hampered by:

- a) Competition with targeted agents
- b) High transplant-related mortality
- c) The lack of well-designed phase II studies
- d) All of the above