We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS BOOK CITATION INDEX INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

18

Intensified Chemotherapy with Stem Cell Support for Solid Tumors in Adults: 30 Years of Investigations Can Provide Some Clear Answers?

Paolo Pedrazzoli[1], Giovanni Rosti[2], Simona Secondino[1], Marco Bregni[3] and Taner Demirer[4]
[1]*Dipartimento Onco-Ematologico, Fondazione IRCCS Policlinico S. Matteo, Pavia,*
[2]*Oncologia Medica, Ospedale Ca' Foncello, Treviso,*
[3]*Dipartimento Ematologico, Istituto Scientifico San Raffaele, Milano,*
[4]*Department of Hematology, Ankara University Medical School, Cebeci Hospital, Ankara,*
[1,2,3]*Italy*
[4]*Turkey*

1. Introduction

High-dose chemotherapy (HDC) with autologous hematopoietic stem cell transplantation (AHSCT) was first introduced as an experimental treatment for solid tumours in the late seventies (1). The basic line for such treatment was extremely simple: can grams work where milligrams fail? Initial data were from pediatric tumors, but soon after an incredible amount of data came from germ cell tumor (GCT), breast carcinoma (BC), small cell lung cancer (SCLC), ovarian cancer and nearly all tumor types have been treated, many of them reported as anecdotal.

After more than thirty years of investigations we are now in the position of giving a lookout of what happened and why some questions received an answer and why others did not. The "rush to transplantation" in the early times led to thousands of patients (pts) treated with such modality, BC being the most preferred indication with nearly 2,000 pts per year in the late nineties only in Europe (2). Unfortunately, the vast majority of those pts have been treated outside clinical trials, so the level of evidence for years remained at the lowest level. Nevertheless some important studies have been conducted and at least for some tumor types some robust data have been provided.

This article will try to clarify what happened and where we are now in this still fascinating and probably not exhausted field. We will first consider BC due to the huge amount of data available, and then other tumors for which HDC has been widely utilized.

2. Breast cancer

Several nonrandomized studies conducted in the eighties and early nineties demonstrated considerable improvements for pts with BC receiving HDC (3-5). This led to the premature

acceptance of HDC as a treatment option for high risk adjuvant and metastatic BC, and the number of transplants performed worldwide consistently increased during the nineties (2). By the mid-1990s, BC had become the most common indication for AHSCT in North America and Europe. There followed a phase of disillusion after premature reports of some randomized studies not showing significant overall survival (OS) benefit of HDC and after a case of scientific misconduct (6). The scene was set for the demise of HDC in BC, and in more recent years the number of procedures has diminished and in fact abandoned by the vast majority of Centers (7). In more recent years, new information provided from mature phase III trials and a metaanalysis (8-10) suggest that HDC may still have a role in subgroups of pts with BC.

2.1 Adjuvant setting

The body of evidence consists of 15 randomized studies including more than 6,200 pts (10,11) Three of those have to be considered pilot or feasibility studies with less than 100 pts each (12-14). The Scandinavian Study by Bergh et al (15) is the only one with a poorer survival of the HDC arm. However, because of the unusual design of the study (chemotherapy (CT) in the control arm tailored to individual tolerance), pts in the control arm received a significantly higher total dose of CT and had a higher incidence of treatment-related leukemia and myelodysplastic syndromes.

Three important trials conducted in the era of peripheral blood stem cells, and comparing HDC with appropriate control have been recently published. The transplant-related mortality (TRM) in these studies ranged from 0 to 1%. The IBCSG reported a PFS advantage of intensified doxorubicin-cyclophosphamide regimen over conventional antracyclin-based CT pts with high risk of relapse harboring ER+ tumors (16). The largest study of HDC in BC, recently updated with a follow up of 7 years (8), has shown a clear advantage in favour of HDC in RFS in women with > 9 positive nodes and in OS in pts with > 3 positive nodes and Her2 negative tumors. Finally, Nitz et al (9) demonstrated a significant RFS and OS improvement in pts with high-risk BC (>9 positive nodes) with a tandem high-dose regimen with no treatment-related mortality.

Some have argued that HDC have been so far compared with "old fashion" conventional treatments. Among new antineoplastic agents introduced in the last two decades, taxanes, the only ones to show additional benefit to conventional antracycline-based combinations, produce limited survival advantage, if any, in the higher risk population for nodal status, i.e. > 3 LN (17,18). Moreover, taxanes are more effective in the HER2 positive pts (17), which is the population not likely to benefit from HDC alkylating agents. The only targeted therapy currently utilized in the adjuvant setting of BC (trastuzumab) is effective (and approved) in HER2+ disease. It is true that taxanes and targeted therapies were not included in the control arms. But they were not included in the HDC arms as well

In summary, the following considerations in the adjuvant setting can be drawn:

1. Most of the studies of HDC show an advantage in RFS, regarded as the primary end-point in the adjuvant setting by oncologists, while an OS benefit was observed in two modern trials comparing HDC with appropriate control and utilizing blood stem cells.
2. The Dutch study (8) and the recent metaanalysis by Berry at al. (10) provide evidence that only pts with Her2 negative tumors do benefit from HDC. This observation confirms the conclusion of several retrospective analyses that Her2 positive tumors should probably not receive HD alkylating CT. Moreover, if one assumes that 25-30% of

pts in randomized studies have HER2 positive disease, these pts will not benefit from HDC and will in fact do worse if effective antracycline-based CT is withheld, then any benefit from HDC for the HER2 negative tumors will be invisible in the final outcome.

3. While difficult to perform due to the limited interest of the pharmaceutical companies, future studies on HDC should concentrate on populations likely to benefit most from this form of therapy and on regimens with low mortality rate.

2.2 Metastatic BC

Individual studies have suggested that age/menopausal status, hormone-receptor status or HER-2/*neu* expression, tumor load, and chemosensitivity may be predictive of the benefits of HDC (19-22).

When looking at prospective randomized studies An equivalent or better EFS has been shown in all trials but, only one published as full report could demonstrate an OS advantage (11). A recent metaanalysis of phase III studies failed to demonstrate a survival advantage of HDC in MBC (23). Also for MBC it would be important to identify pts, if any, that are likely to benefit most from HDC. In particular, HDC appears to be effective in stage IV pts who were rendered free of macroscopic disease by previous therapy or in patients with oligometastatic disease (19,22). It clearly comes out from two large retrospective analysis (2,24) that a significant proportion of patients undergoing HDC after achieving response from conventional treatments are long term (>5 years) disease free survivors. Such results suggest that HDC with AHSCT can cure a subset of patients with MBC.

Finally, as observed in the adjuvant setting, also stage IV pts with HER2 positive tumors derive no benefit from high-dose alkylating agents (19). It requires to be demonstrated whether the use of non-alkylating drugs, including taxanes, antracycline and mitoxantrone (24, 32), in HDC regimens might prove effective in subset of pts with HER2 positive or with other biological tumor characteristics (29).

Also in the setting of metastatic disease, randomized studies in selected patient populations are necessary to define the exact role of HDC.

2.3 Small cell lung carcinoma (SCLC)

Probably due to its high chemosensitivity and its poor prognosis, SCLC has been the first adult tumor to be tested with HDC in a relative large number of pts. The first attempts have been very pioneristic, with pts usually grafted after first or subsequent lines with poor performance status and in a chemorefractory phase of their diseases.

After several small studies conducted in the eighties and early nineties showing that HDC might have a role in selected patients (25), The EBMT launched the first and so far only randomized study where pts with limited and extensive disease ≤ 2 metastatic sites were given either conventional CT or a multiple transplant program, i.e. three high-dose ICE (ifosfamide, carboplatin and etoposide) shots (26). This international study, enrolling 145 pts (half of the planned number), showed no significantly improved 3-year PFS or OS benefit of increasing the dose–intensity, the peak-dose or the total dose of ICE. It is important to note that 9% of pts in the HDC arm died of therapy-related toxicity, a data that other than being unacceptable today, can *per se* explain the lack of favourable results of this study.

At present the number of pts receiving HDC worldwide is anecdotal. The role of dose intensification in the treatment of SCLC would deserve further evaluation, taking into consideration also the very poor progress obtained in such tumor in the last decades and the so far pessimistic scenario of target therapy in this disease (27).

2.4 Germ cell tumors (GCT)

Because of the extremely high chemosensitivity of GCTs, the concept of HDC in this disease has been rapidly developed worldwide and intensively investigated. Clinical trials have been performed in a variety of settings, ranging from resistant or absolute refractory disease to chemosensitive relapse. The role of dose-intensification with stem cell support has also been explored as a part of first-line strategy for patients at higher risk of recurrence. This issue has been recently comprehensively reviewed by Simonelli et al (28) who suggest that the role of HDC in GCTs remains controversial mainly due to the heterogeneity of patient population and treatment approaches, the lack of well-defined prognostic variables and the limited number of randomized trials conducted.

HDC with stem cell rescue cannot be proposed for poor risk patients, neither as front-line therapy nor as consolidation, in patients achieving response by conventional CT. The two randomized studies conducted in this patient population (29,30) failed to demonstrate an OS benefit. Albeit supported by limited data, first line "consolidation" HDCT may be considered in selected patients with chemosensitive primary mediastinal disase (31,32). Intensified treatments has been more widely investigated as a salvage therapy for patients with an incomplete response to initial CT and for those with relapsed GCTs. Despite the robust data from the Indiana group (33) and from other retrospective/phase II studies (28), the role of HDCT as second line treatment for relapsed GCTs, remains today uncertain. Also in view of the very recent data produced by Lorch et al (34), the most pressing issues in GCT treatment are defining standards of HDC and optimizing outcomes of salvage treatment. The recently proposed TIGER study, comparing four cycles of conventional dose TIP versus paclitaxel/ifosfamide followed by multiple HD-CE as first line salvage treatment in refractory/relapsed GCT patients, goes in this direction (35). HDC should be considered a treatment option for patients that are (primary) refractory to platinum-based CT or for those with a first or further relapse (33,36,37). Multiple intensified cycles with carboplatin/etoposide (33,38) is recommended as the standard HD treatment also due to concern that using a three-drug regimen would require dose reductions of the two most active drugs in this setting.

2.5 Ovarian carcinoma

Early reports of HDC for ovarian carcinoma dealt with pts with resistant or refractory disease. Several small phase II studies have shown activity of HDC, but responses were generally short lasting (39). These early studies were extremely heterogeneous in terms of pts' selection, use of chemotherapeutic agents and schedule of administration.

Stiff et al reported a single centre experience in 100 pts with relapsed or persistent disease treated with various HDC regimens (40). The median OS were 9,6 and 23.1 months for pts with platinum-resistant and platinum-sensitive disease, respectively, leading to the conclusion that platinum sensitivity and tumor bulk are the two most important predictors of survival following HDC. Two large retrospective analyses including data from the European and American registries database (251 and 421 patients, respectively) suggested a survival benefit in pts receiving HDC as consolidation following conventional first line CT (41) or being in remission at transplant (42).

In late 1998 the EBMT launched an international randomised trial of multi-cycle HDC in optimally debulked pts. Control arm consisted of 6 courses of standard dose carboplatin-paclitaxel. Later on this study merged with a similar German trial. The final analysis of this

combined study included 149 patients, half of the planned population providing evidence of no benefit of HDC on survival (43). Two other randomised trials, conducted by the Gynaecological Oncology Group and by a Finnish group closed early due to poor recruitment. At present no HDC studies are ongoing in ovarian cancer.

2.6 Sarcoma

In *soft tissue sarcoma* (STS) several phase I and II studies have been conducted (39, 44) but, because of the heterogeneity of study population and histology, no evidence-based conclusions could be extrapolate. Recently, the only randomized study to date has been published by the French sarcoma group. This trial failed to show an OS advantage for advanced STS patients treated with dose-intensified chemotherapy with stem cell support (45).
In the highly chemosensitive *Ewing family of tumors* (EFT), a rare disease in adults, data are far more convincing both in locally advanced and metastatic disease (46-48). First line EFT pts with good responding disease, i.e. complete-partial response, as well as patients with sensitive relapse are good candidates to be considered for HDC, whenever possible within controlled studies.
Finally, evidence of HDC role in *rhabdomyosarcomas* and *osteosarcomas* is still missing (49,50).

3. Conclusion

What we can take from the bulk of clinical studies performed over the last 30 years, which unfortunately include a limited number of randomized studies, is that greatly increasing the total dose of CT may prove effective in subgroup of pts with defined clinical and biological characteristics, as suggested for BC. Many oncologists believe that is not quite enough and suggest that this approach should cease while we entered the era of targeted therapies (51). However, such a conclusion could be just as premature and thoughtless as the uncritical use of HDC that was so common 15 years ago.
HDC with AHSCT has become a safe and reasonably well-tolerated treatment modality (52) that can even be administered in the outpatient setting. Moreover, the prognosis of solid tumors discussed in this article has changed very little in the past decades, as novel targeted therapies had a clear impact only in the subset of pts with BC overexpressing HER2 (53,54).
We believe that, instead of simply giving up on a potential treatment modality, it is more logical and practical to refine and improve this existing therapy in addition to developing new approaches in the clinical trial setting (55). Improvement of treatment of solid tumor may well come, in the future, by integrating intensified CT, being *per-se* capable of remarkable and rapid tumor regression, with novel treatment strategies (i.e. immunotherapy or target-specific therapy) for their potential to eliminate residual disease (56,57)
In conclusion, data available to date do not support, outside controlled trials, the use of HDC with AHSCT for solid tumors in adults, with the possible exception of highly selected, well informed pts with GCTs, BC and EFT.

4. References

[1] Skipper HE. Dose intensity versus total dose of chemotherapy: An experimental basis. In: De Vita VT, Hellman S, Rosenberg SA eds. Important Advances in Oncology. Philadelphia Lippincott, 1990, pp 43-64.

[2] Pedrazzoli P, Ferrante P, Kulekci A, Schiavo R, De Giorgi U, Carminati O, et al: Autologous hematopoietic stem cell transplantation for breast cancer in Europe: critical evaluation of data from the European Group for Blood and Marrow Transplantation (EBMT) Registry 1990-1999. Bone Marrow Transplant 32: 489-494, 2003.

[3] Eder J, Antman K, Peters W, Henner WD, Elias A, Shea T, et al: High-dose combination alkylating agent chemotherapy with autologous bone marrow support for metastatic breast cancer. J Clin Oncol 4:1592-1597, 1986

[4] Peters WP, Ross M, Vredenburgh JJ, Meisenberg B, Marks LB, Winer E, et al: High-dose chemotherapy and autologous bone marrow support as consolidation after standard-dose adjuvant therapy for high-risk primary breast cancer. J Clin Oncol 11:1132-1143, 1993

[5] Gianni AM, Siena S, Bregni M, Di Nicola M, Orefice S, Cusumano F, et al: Efficacy, toxicity, and applicability of high-dose sequential chemotherapy as adjuvant treatment in operable breast cancer with 10 or more involved axillary nodes: five-year results. J Clin Oncol 15:2312-21, 1997

[6] Weiss RB, Rifkin RM, Stewart FM, Theriault RL, Williams LA, Hermann AA, et al: High-dose chemotherapy for high-risk primary breast cancer: an on-site review of the Bezwoda study. Lancet 355:999-1003, 2000

[7] Gratwohl A, Schmid O, Baldomero H, Horisberger B, Urbano-Ispizua A: Haematopoietic stem cell transplantation (HSCT) in Europe 2002. Changes in indication and impact of team density. A report of the EBMT activity survey. Bone Marrow Transpl 34:855-875, 2004

[8] Rodenhuis S, Bontenbal M, van Hoesel QG, Smit WM, Nooij MA, Voest EE, et al: Efficacy of high-dose alkylating chemotherapy in HER2/neu-negative breast cancer. Ann Oncol 17:588-596, 2006

[9] Nitz UA, Mohrmann S, Fisher J, Lindemann W, Berdel WE, Jackisch C, et al: Comparison of rapidly cycled tandem high-dose chemotherapy plus peripheral-blood stem-cell support versus dose-dense conventional chemotherapy for adjuvant treatment of high-risk breast cancer: results of a multicentre phase III trial. Lancet 366:1935-1944, 2005

[10] Berry DA, Ueno NT, Johnson MM et al. High-dose chemotherapy with autologous stem cell support as adjuvant therapy in breast cancer: overview of 15 randomized trials J Clin Oncol, in press

[11] Pedrazzoli P, Ledermann JA, Lotz JP, Leyvraz S, Aglietta M, Rosti G et al: High dose chemotherapy with autologous hematopoietic stem cell support for solid tumors other than breast cancer in adults. Ann Oncol 17:1479-1488, 2006

[12] Hanrahan EO, Broglio K, Frye D, Buzdar AU, Theriault RL, Valero V, et al: Randomized trial of high-dose chemotherapy and autologous hematopoietic stem cell support for high-risk primary breast carcinoma: follow-up at 12 years. Cancer 106:2327-36, 2006.

[13] Schrama JG, Faneyte IF, Schronagel JH, Baars JW, Pertese JL, van de Vijver MJ, et al: Randomized trial of high-dose chemotherapy and hematopoietic progenitor-cell support in operable breast cancer with extensive lymph node involvement: final analysis with 7 years of follow-up. Ann Oncol 13:689-698. 2002.

[14] Tokuda Y, Tajima T, Narabayashi M, Takeyama T, Watanabe T, Fukutomi T, et al: Randomized phase 3 study of high-dose chemotherapy (HDC) with autologous stem cell support as consolidation in high-risk postoperative breast cancer: Japan Clinical Oncology (JCOG9208). Proc ASCO 20:38a, 2001 (abstr)

[15] Bergh J, Wiklund T, Erikstein B, Lidbrink E, Lindman H, Malmström P, et al: Tailored fluorouracil, epirubicin and cyclophosphamide compared with marrow-supported high-dose chemotherapy as adjuvant treatment for high-risk breast cancer: a randomized trial. Scandinavian Breast Group 9401 study. Lancet 356:1384-1391,2000

[16] Basser RL, O'Neill A, Martinelli G, Green MD, Peccatori F, Cinieri S, et al: Multicycle dose-intensive chemotherapy for women with high-risk primary breast cancer: results of International Breast Cancer Study Group Trial 15-95. J Clin Oncol 24:370-8, 2006

[17] Martin M, Pienkowski T, Mackey J Pawlicki M, Guastalla JP, Weaver C, et al: Adjuvant docetaxel for node-positive breast cancer. N Engl J Med 352:2302-2313, 2005

[18] Henderson IC, Berry DA, Demetri GD et al. Improved outcomes from adding sequential Paclitaxel but not from escalating Doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. J Clin Oncol. 2003 Mar 15;21(6):976-83.

[19] Nieto Y, Nawaz S, Jones RB, Shpall EJ, Cagnoni PJ, Mcweeney PA, et al: Prognostic model for replapse after high-dose chemotherapy with autologous stem-cell transplantation for stage IV ologometastatic breast cancer. J Clin Oncol 20: 707-718, 2002

[20] Kurian S, Qazilbash M, Fay J, Wolff S, Herzig R, Hobbs G, et al: Complete Response after High-Dose Chemotherapy and Autologous Hemopoietic Stem Cell Transplatation in Metastatic Breast Cancer Results in Survival Benefit. Breast J 12:531-235, 2006

[21] Diallo-Danebrock R, Ting E, Gluz O, Herr A, Mohrmann S, Geddert H, et al. Protein expression profiling in high-risk breast cancer patients treated with high-dose or conventional dose-dense chemotherapy. Clin Cancer Res 13: 488-497, 2007

[22] Montemurro F, Rondón G, Ueno NT et al. Factors affecting progression-free survival in hormone-dependent metastatic breast cancer patients receiving high-dose chemotherapy and hematopoietic progenitor cell transplantation: role of maintenance endocrine therapy. Bone Marrow Transplant 29: 2002; 861-866.

[23] DA Berry, NT Ueno, Johnson MM et al. High-dose chemotherapy with autologous hematopoietic stem cell transplantation versus standard-dose chemotherapy: Overview of individual patient data from six randomized metastatic breast cancer trials. J Clin Oncol, in press

[24] Martino M, Ballestrero A, Zambelli A, et al, on behalf of GITMO. Long term survival in patients with metastatic breast cancer receiving intensified chemotheapy and stem cell rescue: data from the italian registry. Submitted

[25] Elias A. Hematopoietic stem cell transplantation for small cell lung cancer. Chest 116: (s6):531S-538S,1999

[26] Leyvraz S, Pampallona S, Martinelli G, et al: A threefold dose intensity treatment with ifosfamide, carboplatin, and etoposide for patients with small cell lung cancer: a randomized trial. J Natl Cancer Inst. 100: 533-41, 2008.

[27] Rosti G, Carminati O, Monti M, et al. Chemotherapy advances in small cell lung cancer. Ann Oncol 17(s5):v99-102, 2006

[28] M Simonelli M, G Rosti G, GL Banna GL, P Pedrazzoli P. Intensified chemotherapy with stem cell rescue in germ-cell tumors. Ann Oncol, in press

[29] Motzer RJ, Nichols CJ, Margolin KA et al. Phase III randomized trial of conventional-dose chemotherapy and autologous hematopoietic stem-cell rescue as first-line treatment for patients with poor-prognosis metastatic germ cell tumors. J Clin Oncol 25: 247-256, 2007

[30] Daugaard G, Skoneczna IA, Aass N, et al. A randomized phase III study comparing standard dose BEP with sequential high-dose cisplatin, etoposide, ifosfamide (VIP) plus stem cell support in males with poor prognosis germ cell cancer (GCC): An intergroup study of EORTC, GTCSG, and Grupo Germinal (EORTC 30974). Proc Am Soc Clin Oncol 2010 28: 15s, (suppl; abstr 4512).

[31] Bokemeyer C, Schleucher N, Metzner B et al. First-line sequential high-dose VIP chemotherapy with autologous transplantation for patients with primary mediastinal nonseminomatous germ cell tumours: a prospective trial. Br J Cancer 89: 29–35, 2003.

[32] Rosti G, De Giorgi U, Wandt H et al. First-line high-dose chemotherapy for patients with poor prognosis extragonadal germ cell tumors: the experience of the European Bone Marrow Transplantation (EBMT) Solid Tumors Working Party. Bone Marrow Transplant 34: 1033–1037, 2004

[33] Einhorn LH, Williams SD, Chamness BA et al. High-dose chemotherapy and stem cell rescue for metastatic germ-cell tumors. N Engl J Med 357; 340-348, 2007.

[34] Lorch A, Bascoul-Mollevi C, Kramar A, et al. Conventional-dose versus high-dose chemotherapy as first salvage treatment in male patients with metastatic germ cell tumors: evidence from a large international database. J Clin Oncol. 29: 2178-84, 2011

[35] Pedrazzoli P, De Giorgi U, Bregni M. High-dose chemotherapy (HDCT) and autologous stem cell transplantation in relapsed germ cell tumors: do we need a randomized study? BMT 45 (suppl 2)S30, 2010.

[36] Vaena DA, Abonour R, Einhorn LH: Long-term survival after high-dose salvage chemotherapy for germ cell malignancies with adverse prognostic variables. J Clin Oncol 21: 4100–4104, 2003.

[37] Lorch A, Neubauer A, Hackenthal M, et al. High-dose chemotherapy (HDCT) as second-salvage treatment in patients with multiple relapsed or refractory germ-cell tumors. Ann Oncol 21: 820-825, 2010.

[38] Kondagunta GV, Bacik J, Sheinfeld J et al. Paclitaxel plus ifosfamide followed by high-dose carboplatin plus etoposide in previously treated germ cell tumors. J Clin Oncol 25: 85-90, 2007.

[39] Pedrazzoli P, Ledermann JA, Lotz JP, et al: High dose chemotherapy with autologous hematopoietic stem cell support for solid tumors other than breast cancer in adults. Ann Oncol 17:1479-1488, 2006

[40] Stiff PJ, Bayer R, Kerger C, Potkul RK, Malhotra D, Peace DJ, et al: High-dose chemotherapy with autologous transplantation for persistent/relapsed ovarian cancer: a multivariate analysis of survival for 100 consecutively treated patients. J Clin Oncol 15: 1309-1317, 1997

[41] Lederman JA, Herd R, Maraninchi D, Viens P, Buclon M, Philip T, et al: High-dose chemotherapy for ovarian carcinoma: long term results from the Solid Tumour Registry of the European Group for Blood and Marrow Transplantation (EBMT). Ann Oncol 12: 639-699, 2001

[42] Stiff P, Veum-Stone J, Lazarus HM, Ayash L, Edwards JR, Keating A, et al: High-dose chemotherapy and autologous stem-cell transplantation for ovarian cancer: an autologous blood and marrow transplant registry. Ann Intern Med 133: 504-515, 2000

[43] Möbus V, Wandt H, Frickhofen N, et al Phase III trial of high-dose sequential chemotherapy with peripheral blood stem cell support compared with standard dose chemotherapy for first-line treatment of advanced ovarian cancer: intergroup trial of the AGO-Ovar/AIO and EBMT. J Clin Oncol. 25:4187-93, 2007.

[44] Peinemann F, Smith LA, Kromp M, et al. Autologous hematopoietic stem cell transplantation following high-dose chemotherapy for non-rhabdomyosarcoma soft tissue sarcomas. Cochrane Database Syst Rev. 2011 Feb 16;(2): CD008216.

[45] Bui-Nguyen B, Ray-Coquard I, Chevreau C, et al.High-dose chemotherapy consolidation for chemosensitive advanced soft tissue sarcoma patients: an open-label, randomized controlled trial. Ann Oncol. 2011 Jun 7. [Epub ahead of print]

[46] Laurence V, Pierga JY, Barthier S, Long-term follow up of high-dose chemotherapy with autologous stem cell rescue in adults with Ewing tumor. Am J Clin Oncol 28:301-9, 2005

[47] Ladenstein R, Pötschger U, Le Deley MC, Primary disseminated multifocal Ewing sarcoma: results of the Euro-EWING 99 trial. J Clin Oncol 28:3284-91, 2010.

[48] Ferrari S, Sundby Hall K, et al. Nonmetastatic Ewing family tumors: high-dose chemotherapy with stem cell rescue in poor responder patients. Results of the Italian Sarcoma Group/Scandinavian Sarcoma Group III protocol. Ann Oncol 22:1221-7, 2011.

[49] Admiraal R, van der Paardt M, Kobes J, et al. High-dose chemotherapy for children and young adults with stage IV rhabdomyosarcoma. Cochrane Database Syst Rev. 2010 Dec 8;(12):CD006669.

[50] Fagioli F, Biasin E, Mereuta OM et al. Poor prognosis osteosarcoma: new therapeutic approach. Bone Marrow Transplant 41 Suppl 2:S131-4, 2008.

[51] Hortobagyi GN: What is the role of high-dose chemotherapy in the era of targeted therapies? J Clin Oncol 22: 2263-2266, 2004

[52] Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, et al: Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 353:1659-1672, 2005.

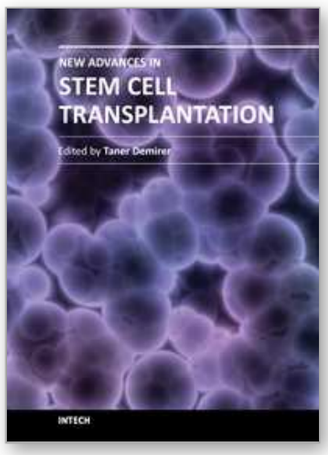
[53] Geyer CE, Forster J, Lindquist D, Chan S, Romieu CG, Pienkowski T, et al: Lapatinib plus Capecitabine for HER2-Positive Advanced Breast Cancer. N Engl J Med 355:2733-2743, 2006.

[54] Marino P, Roché H, Moatti JP; PEGASE Group. High-dose chemotherapy for patients with high-risk breast cancer: a clinical and economic assessment using a quality-adjusted survival analysis. Am J Clin Oncol 31:117-124, 2008

[55] Cheng YC, Ueno NT. Is high-dose chemotherapy with autologous hematopoietic stem cell transplantation in breast cancer patients a done deal? Womens Health 6:481-485, 2010

[56] Siena S: Towards the integration of hematopoietic stem cells into therapy of breast cancer? Haematologica 84:865-867,1999

[57] Cheng YC, Rondón G, Sanchez LF et al. Interleukin-2 and granulocyte-macrophage-colony-stimulating factor immunomodulation with high-dose chemotherapy and autologous hematopoietic stem cell transplantation for patients with metastatic breast cancer. Int J Hematol 90: 627-634, 2009.



New Advances in Stem Cell Transplantation
Edited by Prof. Taner Demirer

ISBN 978-953-51-0013-3
Hard cover, 582 pages
Publisher InTech
Published online 24, February, 2012
Published in print edition February, 2012

This book documents the increased number of stem cell-related research, clinical applications, and views for the future. The book covers a wide range of issues in cell-based therapy and regenerative medicine, and includes clinical and preclinical chapters from the respected authors involved with stem cell studies and research from around the world. It complements and extends the basics of stem cell physiology, hematopoietic stem cells, issues related to clinical problems, tissue typing, cryopreservation, dendritic cells, mesenchymal cells, neuroscience, endovascular cells and other tissues. In addition, tissue engineering that employs novel methods with stem cells is explored. Clearly, the continued use of biomedical engineering will depend heavily on stem cells, and this book is well positioned to provide comprehensive coverage of these developments.

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen