JBUON 2017; 22(2): 306-311
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

REVIEW ARTICLE

An overview of high dose chemotherapy with autologous stem cell rescue for germ cell tumors in current practice

Sukru Ozaydın[1], Ugur Sahin[2], Nuri Karadurmus[1], Fikret Arpaci[3], Taner Demirer[2]

[1]Gulhane Military Medical Academy, Department of Medical Oncology, Etlik, Ankara, Turkey; [2]Ankara University Medical School, Department of Hematology, Ankara, Turkey; [3]Liv Hospital, Department of Medical Oncology, Ankara, Turkey

Summary

Testicular cancer is a frequent tumor of adolescent and young adult males. Chemotherapy has been reported to provide cure rates as high as 80% even in the presence of advanced testicular cancer. Studies regarding testicular cancer started after the advent of high dose chemotherapy (HDC) plus atologous stem cell rescue (ASCR) for the treatment of solid tumors in 1980s. Testicular cancer is highly responsive to HDC. Einhorn et al. have reported long-lasting remissions reaching up to 40% among patients with platinum-refractory disease. However, the present prospective randomized studies are heterogeneous in terms of patient characteristics and methodology, therefore superiority of HDC plus ASCR to conventional chemotherapies could not be proven. The results of the TIGER study, which is a recent prospective randomized study being conducted by the European Organisation for Research and Treatments in Cancer (EORTC) and the European Society for Blood and Marrow Transplantation (EBMT) aiming to compare HDC plus ASCR to conventional chemotherapy are eagerly expected. In this review, we will evaluate the current use of HDC plus ASCR in patients with relapsed or refractory germ cell tumors.

Key words: *autologous stem cell transplantation, germ cell tumors*

Introduction

Testicular cancer constitutes 1% of all cancers and 5% of urological cancers in males. It is the most common tumor in 15-35 year-old men. In contrast to a historical annual mortality of 90% for metastatic testicular cancer 50 years ago, the advent of cisplatin and other chemotherapeutics has provided a cure rate of over 90% [1].

Testicular tumors are classified into favorable, intermediate and poor prognostic categories by the International Germ Cell Cancer Collaborative Group according to site of the primary tumor, presence of metastasis and serum tumor marker levels [2]. The standard treatment for metastatic testicular cancer involves 3 to 4 cycles of cisplatin, etoposide and bleomycin (BEP) regimen. BEP provides cure in over 90% of patients in the favorable group, whereas the cure rates in the intermediate and poor prognostic groups are 75% and 50%, respectively [3].

Disease remission is possible after second or even third line chemotherapy among patients who do not sustain long-term remissions after the first line. Vinblastine, ifosfamide and cisplatin (VeIP) [4] or cisplatin, ifosfamide and paclitaxel (TIP) [5] regimens may provide long-lasting remissions in relapsed and/or refractory testicular cancer.

HDC with ASCR has been used in testicular cancer as an attractive treatment modality since the 1980s after the advent of HDC plus ASCR for the treatment of various solid tumors [6-15]. Taking into consideration the chemo-sensitivity of germ cell tumors, their steep dose-response curves, rarity of bone marrow involvement, younger patient age at diagnosis and wide therapeutic range of

Correspondence to: Taner Demirer, MD, FACP. Professor of Medicine and Hematology/Oncology, Ankara University Medical School, Department of Hematology, Cebeci Hospital, Ankara 06220, Turkey. Tel: +90 532 3251065, Fax: +90 312 4663717, E-mail: demirer@medicine.ankara.edu.tr
Received: 09/09/2016; Accepted: 04/10/2016

drugs, testicular cancer was accepted as a good model for use of HDC. However, HDC also has an important dose limiting toxicity, namely myelosuppression [16-22]. Since long-lasting responses could not be proved in earlier studies involving cyclophosphamide and etoposide containing regimens [23,24], more studies have focused on high-dose carboplatin and etoposide containing regimens and resulted in more successful outcomes. Cyclophosphamide and ifosfamide might also be used as an adjunct to carboplatin and etoposide in the spectrum of HDC plus ASCR regimens. According to EBMT registry, germ cell tumors constituted the 27% of all reported HDC plus ASCR therapies for solid tumors between 2005 and 2010 [25].

The purpose of this review was to outline the current indications and clinical use, as well as the efficacy of HDC plus ASCR in the treatment of germ cell tumors in view of the relevant scientific evidence, considering that in our Center - Gulhane Military Medical Academy - germ cell tumors are frequently seen and treated with conventional chemotherapy as well as HDC plus ASCT, if needed.

High-dose chemotherapy as front-line treatment in poor risk patients

The first studies on HDC as front-line treatment in poor risk patients were conducted just after the demonstration of its efficacy in testicular cancer. Chevreau et al. compared the efficacy of 4 courses of vinblastine, etoposide, bleomycin and cisplatin (PVeBV) to one course of modified PVeBV followed by high-dose etoposide, cyclophosphamide and cisplatin (PEC). The 2-year overall survival (OS) rates were 82 vs 60% within a median follow-up of 30 months in the the conventional therapy and HDC plus ASCR arms, respectively. However, this difference in favor of the conventional treatment did not reach statistical significance [26]. Droz et al. also reported similar OS rates within a median follow-up of 9.7 years [27].

A phase II study involving poor risk germ cell tumors compared observation after conventional chemotherapy vs high-dose carboplatin and etoposide plus ASCR after 2 courses of vinblastine, cyclophosphamide, dactinomycin, bleomycin, cisplatin (VAB-6). Although not statistically significant, HDC plus ASCR yielded favorable survival rates when compared to observation after conventional therapy [28].

A phase III trial of HDC plus ASCR in testicular cancer included intermediate and high risk patients and compared 4 cycles of BEP vs 2 cycles of BEP followed by 2 cycles of high-dose carboplatin, etoposide and cyclophosphamide [29]. Overall response (OR) at 1 year and 2-year OS rates were similar between the two groups. However, a subgroup analysis of patients with an incomplete tumor marker response after 2 cycles of BEP revealed a significantly higher durable complete response (CR) rate (61 vs 34%) and a non-significant improvement in 2-year OS in the HDC plus ASCR arm [29].

A multicenter phase III trial demonstrated a superior progression-free survival (PFS) (44.8 vs 58.2%) and OS rates (72.9 vs 65.5%) with one cycle of cisplatin, etoposide and ifosfamide (VIP) followed by 3 cycles of high-dose VIP plus ASCR among patients with previously untreated metastatic non-seminomatous germ-cell cancers, when compared to 4 cycles of standard VIP regimen. However, the differences were statistically non significant [30].

Currently, the use of HDC plus ASCR as a front-line treatment in poor-risk patients remains an experimental approach.

High-dose chemotherapy as a salvage for relapsed germ cell tumors

Patients relapsing after first-line treatment should be encouraged to participate in clinical studies. Other second-line treatment options include conventional regimens, such as VIP, TIP and VeIP or HDC [31].

The first study regarding second-line treatment included 33 patients with either progressive disease within 4 weeks of cisplatin therapy or treatment failure despite 2 cisplatin-based regimens including a salvage with cisplatin and ifosfamide. The study regimen included infusion of etoposide at a dose of 1200 mg/m^2 and carboplatin at a dose of 1500 mg/m^2 plus ASCR. Of the patients, 39% received one course and the rest 2 courses of HDC plus ASCR. OR rate was 44% and CR was achieved in 24%, which was sustained in 12% of patients beyond one year [32].

In another phase III trial, patients with advanced germ cell tumors failing platinum-based treatment in the first-line received either 4 cycles of cisplatin, ifosfamide and etoposide (or vinblastin) or 3 cycles of the same regimen followed by high-dose carboplatin, etoposide and cyclophosphamide plus ASCR [33]. The two arms yielded similar CR and partial response (PR) rates. However, a significant improvement in PFS was observed among patients who achieved CR in the HDC plus ASCR arm (55 vs 75% at 3 years) but there was

no statistically significant difference between two arms regarding OS rates.

A prospective randomized multicenter trial by the German Testicular Cancer Study Group recruited patients with relapsed or refractory germ cell tumors and was prematurely stopped due to overriding treatment-related mortality with 3 cycles of VIP followed by one cycle of high-dose carboplatin (2,200 mg/m^2), etoposide (1,800 mg/m^2) and cyclophosphamide (6,400 mg/m^2) with ASCR when compared to one cycle of VIP followed by 3 cycles of high-dose carboplatin (1,500 mg/m^2) and etoposide (1,500 mg/m^2) with ASCR [34]. Single or sequential HDC arms had similar results in terms of PFS and OS at one year (49 vs 53% and 61 vs 80%, respectively). In the long-term analyses, single or sequential HDC arms also yielded similar results in terms of PFS and OS (45 vs 47% and 39 vs 49%, respectively, at 5 years) [35]. This study showed that there was no advantage of using sequential HDC compared to single HDC in patients with relapsed or refractory germ cell tumors.

A multicenter retrospective study including patients with relapsed testicular cancer after first-line therapy compared HDC plus ASCR and standard-dose chemotherapy (SDC) [36]. To help in the choice of an optimal strategy, the International Prognostic Factor Study Group performed a large retrospective data collection on 1984 patients from major centers around the world and identified 7 prognostic factors with independent impact on survival rates after first salvage treatment [37]. This analysis, which was done by Lorch et al., showed that patients could reliably be classified into 5 prognostic categories based on prior prognostic classification from very low-risk to very high-risk. Within each of the 5 categories the PFS and OS after SDC and HDC plus ASCR were compared using the Cox model. Overall, 733 patients received SDC and 821 patients received HDC plus ASCR. Both treatment modalities were used with similar frequencies within each prognostic category [36]. In low-risk patients, no difference in OS was observed between the two treatment groups, but in all remaining prognostic groups both PFS and OS were superior for HDC plus ASCR [36]. Significantly higher rates of PFS and OS were achieved with HDC plus ASCR (PFS at 2 years 49.6 vs 27.8% and OS at 5 years 53.2 vs 40.8%, respectively) in patients with intermediate and high-risk relapsed germ cell tumors. In addition, sequential HDC plus ASCR also yielded a superior OS at 5 years (60.6 vs 46.3%) in this analysis. The authors concluded that when the patients are classified as having a low, intermediate, high and very high-risk disease, HDC plus ASCR resulted in a significantly higher OS at 5 years in all groups excluding patients with low-risk disease. This retrospective analysis suggests a benefit for HDC plus ASCR given as intensification of first salvage treatment in patients with germ cell tumors, excluding low risk patients, and supports the prospective efforts that are under way to address the issue of HDC plus ASCR vs SDC in an international prospective randomized phase III trial, the TIGER trial [38].

High-dose chemotherapy as a salvage beyond second-line treatment

In their retrospective review, Einhorn et al. have reported a DFS of 44.9% with a median of 46 months among patients receiving HDC plus ASCR as a third-line or beyond therapy [39]. Another retrospective study included patients scheduled for either single or sequential HDC plus ASCR for testicular cancer relapsing after second-line treatment and reported an OR of 55% and a projected OS rate of 17% at 5 years [40]. Currently, there is no phase III randomized prospective trial showing the efficacy of HDC plus ASCR compared to SDC in this setting.

High-dose chemotherapy in extragonadal germ cell tumors

Extragonadal germ cell tumors constitute 2-5% of all testicular cancers [41,42]. They frequently originate from mediastinum and retroperitoneum and they have a poor prognosis according to International Germ Cell Cancer Consensus Group (IGCCCG) criteria [3].

In a study by the EBMT Solid Tumors Working Party (EBMT-STWP), patients with extragonadal germ cell tumors received high-dose carboplatin and etoposide plus ASCR after induction therapy. The reported CR rate was 77% and DFS 68% in a median follow-up of 50 months [43].

Another retrospective study by EBMT-STWP investigated the efficacy of HDC plus ASCR among patients relapsing after or during primary cisplatin-based chemotherapy. The patients were scheduled for 1 to 4 cycles, the majority 1 cycle, of high-dose carboplatin and etoposide plus ASCR. The reported PFS was 30% in a median follow-up of 58 months [44].

A trial including children with extragonadal germ cell tumors reported an OR of 70% and a DFS of 43% in a median follow-up of 66 months with HDC plus ASCR when performed after either

first relapse or beyond [45].

Extragonadal germ cell tumors are very rare and therefore there is no prospective trial comparing SDC and HDC plus ASCR, head to head, for this subgroup of patients in the literature.

Discussion

Testicular cancer is a chemosensitive tumor. SDC may provide cure in 80% of patients with metastatic disease. Since HDC plus ASCR has been studied in a limited number of phase III trials, some issues are currently obscure. One of the ongoing matters of debate is the number of courses for HDC plus ASCR. The present studies have employed HDC plus ASCR from 1 to 3 courses. The study by Lorch et al. have demonstrated a 4-fold increase in treatment-related mortality with a single course of HDC plus ASCR due to higher doses of cisplatin and etoposide, when compared to sequential HDC using carboplatin and etoposide at lower doses [35]. In concordance, a retrospective review by Lorch et al. has also shown that sequential HDC plus ASCR may provide longer PFS and OS when compared to single course in patients with intermediate, high and very high-risk disease [36].

The second important issue is about the timing of HDC plus ASCR. The studies by Motzer et al. [29] and Daugaard et al. [30] comparing conventional chemotherapy and HDC in the frontline treatment of poor-risk germ cell tumors have yielded similar outcomes with both approaches. Thus, 4 cycles of BEP have been accepted currently as the standard therapy for poor-risk patients.

Finally, the advantage of HDC plus ASCR for relapsed and refractory disease when compared to conventional chemotherapy is being questioned. According to retrospective data by Lorch et al. HDC plus ACSR improved PFS and OS significantly when compared to SDC in patients with intermediate and high-risk disease [36]. On the contrary, in their phase III trial, Pico et al. have reported similar CR, PR, PFS and OS in HDC plus ACSR and SDC arms [33]. But one of the important hurdles of this study was the low accrual rates. Unfortunately, the duration of this prospective European study has just overlapped with the negative results of the prospective breast cancer trials evaluating the efficacy of HDC plus ASCR. Therefore, this study could not reach its target accrual rate and somehow closed early by EBMT-STWP. This lower accrual rate remarkably decreased the statistical power of this study and thus blocked the documentation of OS advantage of HDC plus ASCR in this setting, even if there is any.

Relapsed and refractory germ cell tumors still remain a challenging problem for practicing medical oncologists. Considering these conflicting results, the TIGER trial comparing 4 cycles of TIP with 2 cycles of paclitaxel and ifosfamide followed by 3 cycles of high-dose carboplatin and etoposide plus ASCR has been designed by an international collaboration group [38]. The primary end-point was defined as PFS at 2 years and secondary end-points as OS at 3 years, OR and toxicity profile. The results of this ongoing TIGER trial are expected to clarify the role of salvage HDC plus ASCR as second-line therapy of relapsed and refractory germ cell tumors. Practicing medical oncologists should be encouraged to participate and accrue patients for this pan-European TIGER trial.

In summary, HDC plus ASCR is reserved for patients with relapsing or refractory disease according to recommendations of National Comprehensive Cancer Network (NCCN) guidelines [31]. Currently, according to EBMT guidelines and recommendations HDC plus ASCR in patients with relapsed chemosensitive germ cell tumors remain as a clinical option after a careful assessment of risk and benefits, whereas HDC plus ASCR remains as a standard approach for patients with third-line refractory disease. NCCN and EBMT guidelines are being followed and used in the management of this subgroup of patients in our clinics.

Conflict of interests

The authors declare no confict of interests.

References

1. McGlynn KA, Cook MB. The Epidemiology of Testicular Cancer. In: Foulkes WD, Cooney KA (Eds): Male Reproductive Cancers: Springer; 2010.
2. Albers P, Albrecht W, Algaba F et al. Guidelines on Testicular Cancer: 2015 Update. Eur Urol 2015;68:1054-1068.
3. International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group. J Clin Oncol 1997;15:594-603.
4. Loehrer PJ, Jr., Gonin R, Nichols CR et al. Vinblastine plus ifosfamide plus cisplatin as initial salvage

therapy in recurrent germ cell tumor. J Clin Oncol 1998;16:2500-2504.

5. Kondagunta GV, Bacik J, Donadio A et al. Combination of paclitaxel, ifosfamide, and cisplatin is an effective second-line therapy for patients with relapsed testicular germ cell tumors. J Clin Oncol 2005;23:6549-6555.
6. Demirer T, Petersen FB, Bensinger WI et al. Autologous transplantation with peripheral blood stem cells collected after granulocyte colony-stimulating factor in patients with acute myelogenous leukemia. Bone Marrow Transplant 1996;18:29-34.
7. Demirer T, Buckner CD, Appelbaum FR et al. Busulfan, cyclophosphamide and fractionated total body irradiation for autologous or syngeneic marrow transplantation for acute and chronic myelogenous leukemia: phase I dose escalation of busulfan based on targeted plasma levels. Bone Marrow Transplant 1996;17:491-495.
8. Demirer T, Buckner CD, Appelbaum FR et al. Busulfan, cyclophosphamide and fractionated total body irradiation for allogeneic marrow transplantation in advanced acute and chronic myelogenous leukemia: phase I dose escalation of busulfan based on targeted plasma levels. Bone Marrow Transplant 1996;17:341-346.
9. Peccatori J, Barkholt L, Demirer T et al. Prognostic factors for survival in patients with advanced renal cell carcinoma undergoing nonmyeloablative allogeneic stem cell transplantation. Cancer 2005;104:2099-2103.
10. Demirer T, Celebi H, Arat M et al. Autoimmune thrombocytopenia in a patient with small cell lung cancer developing after chemotherapy and resolving following autologous peripheral blood stem cell transplantation. Bone Marrow Transplant 1999;24:335-337.
11. Kroger N, Damon L, Zander AR et al. Secondary acute leukemia following mitoxantrone-based high-dose chemotherapy for primary breast cancer patients. Bone Marrow Transplant 2003;32:1153-1157.
12. Pedrazzoli P, Ferrante P, Kulekci A 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 2003;32:489-494.
13. Demirer T, Gooley T, Buckner CD et al. Influence of total nucleated cell dose from marrow harvests on outcome in patients with acute myelogenous leukemia undergoing autologous transplantation. Bone Marrow Transplant 1995;15:907-913.
14. Berry DA, Ueno NT, Johnson MM et al. High-dose chemotherapy with autologous hematopoietic stem-cell transplantation in metastatic breast cancer: overview of six randomized trials. J Clin Oncol 2011;29:3224-3231.
15. 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 2006;17:1479-1488.
16. Ladenstein R, Potschger U, Hartman O et al. 28 years of high-dose therapy and SCT for neuroblastoma in Europe: lessons from more than 4000 procedures. Bone Marrow Transplant 2008;41 (Suppl 2):S118-127.
17. Gratwohl A, Baldomero H, Demirer T et al. Hematopoietic stem cell transplantation for solid tumors in Europe. Ann Oncol 2004;15:653-660.
18. Bensinger WI, Demirer T, Buckner CD et al. Syngeneic marrow transplantation in patients with multiple myeloma. Bone Marrow Transplant 1996;18:527-531.
19. Brunvand MW, Bensinger WI, Soll E et al. High-dose fractionated total-body irradiation, etoposide and cyclophosphamide for treatment of malignant lymphoma: comparison of autologous bone marrow and peripheral blood stem cells. Bone Marrow Transplant 1996;18:131-141.
20. Demirer T, Buckner CD, Appelbaum FR et al. High-dose busulfan and cyclophosphamide followed by autologous transplantation in patients with advanced breast cancer. Bone Marrow Transplant 1996;17:769-774.
21. Ueno NT, Rizzo JD, Demirer T et al. Allogeneic hematopoietic cell transplantation for metastatic breast cancer. Bone Marrow Transplant 2008;41:537-545.
22. Holmberg LA, Demirer T, Rowley S et al. High-dose busulfan, melphalan and thiotepa followed by autologous peripheral blood stem cell (PBSC) rescue in patients with advanced stage III/IV ovarian cancer. Bone Marrow Transplant 1998;22:651-659.
23. Blijham G, Spitzer G, Litam J et al. The treatment of advanced testicular carcinoma with high dose chemotherapy and autologous marrow support. Eur J Cancer 1981;17:433-441.
24. Mulder PO, de Vries EG, Koops HS et al. Chemotherapy with maximally tolerable doses of VP 16-213 and cyclophosphamide followed by autologous bone marrow transplantation for the treatment of relapsed or refractory germ cell tumors. Eur J Cancer Clin Oncol 1988;24:675-679.
25. Marco B. Solid tumours in adults. In: Apperley J, Carreras E, Gluckman E, Masszi T (Eds): EBMT-ESH Handbook on Haematopoietic Stem Cell Transplantation (6th Edn.) 2012, pp 526-538.
26. Chevreau C, Droz JP, Pico JL et al. Early intensified chemotherapy with autologous bone marrow transplantation in first line treatment of poor risk non-seminomatous germ cell tumours. Preliminary results of a French randomized trial. Eur Urol 1993;23:213-217; discussion 8.
27. Droz JP, Kramar A, Biron P et al. Failure of high-dose cyclophosphamide and etoposide combined with double-dose cisplatin and bone marrow support in patients with high-volume metastatic nonseminomatous germ-cell tumours: mature results of a randomised trial. Eur Urol 2007;51:739-746; discussion 47-8.
28. Motzer RJ, Mazumdar M, Gulati SC et al. Phase II trial of high-dose carboplatin and etoposide with autologous bone marrow transplantation in first-line therapy for patients with poor-risk germ cell tumors. J Natl Cancer Inst 1993;85:1828-1835.
29. Motzer RJ, Nichols CJ, Margolin KA et al. Phase III randomized trial of conventional-dose chemotherapy

with or without high-dose chemotherapy and autologous hematopoietic stem-cell rescue as first-line treatment for patients with poor-prognosis metastatic germ cell tumors. J Clin Oncol 2007;25:247-256.

30. Daugaard G, Skoneczna I, Aass N et al. A randomized phase III study comparing standard dose BEP with sequential high-dose cisplatin, etoposide, and ifosfamide (VIP) plus stem-cell support in males with poor-prognosis germ-cell cancer. An intergroup study of EORTC, GTCSG, and Grupo Germinal (EORTC 30974). Ann Oncol 2011;22:1054-1061.
31. Clinical Practice Guidelines in Oncology. National Comprehensive Cancer Network, v2.2016, 2016. at http://www.nccn.org/professionals/physician_gls/pdf/testicular.pdf.
32. Nichols CR, Tricot G, Williams SD et al. Dose-intensive chemotherapy in refractory germ cell cancer--a phase I/II trial of high-dose carboplatin and etoposide with autologous bone marrow transplantation. J Clin Oncol 1989;7:932-939.
33. Pico JL, Rosti G, Kramar A et al. A randomised trial of high-dose chemotherapy in the salvage treatment of patients failing first-line platinum chemotherapy for advanced germ cell tumours. Ann Oncol 2005;16:1152-1159.
34. Lorch A, Kollmannsberger C, Hartmann JT et al. Single versus sequential high-dose chemotherapy in patients with relapsed or refractory germ cell tumors: a prospective randomized multicenter trial of the German Testicular Cancer Study Group. J Clin Oncol 2007;25:2778-2784.
35. Lorch A, Kleinhans A, Kramar A et al. Sequential versus single high-dose chemotherapy in patients with relapsed or refractory germ cell tumors: long-term results of a prospective randomized trial. J Clin Oncol 2012;30:800-805.
36. 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 2011;29:2178-2184.
37. International Prognostic Factors Study Group, Lorch A, Beyer J, Bascoul-Mollevi C et al. Prognostic factors in patients with metastatic germ cell tumors who experienced treatment failure with cisplatin-based first-line chemotherapy. J Clin Oncol 2010;28:4906-4911.
38. Feldman DR, Huddart R, Hall E et al. Is high dose therapy superior to conventional dose therapy as initial treatment for relapsed germ cell tumors? The TIGER Trial. J Cancer 2011;2:374-377.
39. Einhorn LH, Williams SD, Chamness A et al. High-dose chemotherapy and stem-cell rescue for metastatic germ-cell tumors. N Engl J Med 2007;357:340-348.
40. 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 2010;21:820-825.
41. Collins DH, Pugh RC. Classification and Frequency of Testicular Tumours. Br J Urol 1964;36 (Suppl):1-11.
42. Hainsworth JD, Greco FA. Extragonadal germ cell tumors and unrecognized germ cell tumors. Semin Oncol 1992;19:119-127.
43. 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 2004;34:1033-1037.
44. De Giorgi U, Demirer T, Wandt H et al. Second-line high-dose chemotherapy in patients with mediastinal and retroperitoneal primary non-seminomatous germ cell tumors: the EBMT experience. Ann Oncol 2005;16:146-151.
45. De Giorgi U, Rosti G, Slavin S et al. Salvage high-dose chemotherapy for children with extragonadal germ-cell tumours. Br J Cancer 2005;93:412-417.