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ORIGINAL ARTICLE

What is the optimal high-dose treatment following autologous stem cell transplantation in relapsed or refractory germ cell cancer: a retrospective comparison of high-dose ICE and high-dose CE

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Summary

Purpose: *Testicular cancer is the most commonly diagnosed solid organ malignancy in 15 to 35 year-old men with 1% incidence among all malignancies. Sixty percent of patients with mild and poor-risk factors need additional treatments. Starting in 1980s, high dose chemotherapy regimens (HDCT) that were not applicable before due to hematological toxicity have been brought into use, and survival and cure possibility have increased. To date, no randomized trial has been conducted to demonstrate superiority of high-dose chemotherapy protocols used for autologous stem cell transplantation (ASCT). Our study aims to compare two commonly used HDCT regimens for a long period, with real-life data.*

Methods: *Approval for thiss retrospective study was obtained from the ethics committee of Gülhane Training and Research Hospital. Fifty refractory testicular cancer patients above 18 years were treated with HDCT and ASCT at Gülhane Training and Research Hospital (January 2011-July 2018).*

Results: *Fifty metastatic, refractory testicular carcinoma patients with a median age of 34 were included in the study. Ninety per cent of the cases had stage III disease at diagnosis. Except for 8 patients (16%) at mild risk group, all the other patients were at high risk. CE was used as salvage treatment for half of the patients and ICE was used for the other half. Four patients responded completely and 30 responded partially to ASCT. Post transplantation median progression-free survival (PFS) was 22 months. Median overall survival (OS) in the general population was 223.4 months (76.1-370.7). Although there was a difference in OS between chemotherapy groups, the difference was not statistically significant. The mean duration of engraftment in patients treated with CE was 11.2 ± 2.3 days, while in patients receiving ICE it was 15.5 ± 2.1 days. This difference between chemotherapy groups was statistically significant (p<0.001).*

Conclusion: *For patients with relapsed/refractory germ cell tumor high dose carboplatin/etoposide and high dose ifosfamide/carboplatin/etoposide regimens were both safe and effective treatments.*

Key words: *Germ cell, relapsed, refractory, high dose, stem cell transplantation, autologous*

Introduction

Testicular cancer is the most commonly diagnosed solid organ malignancy in 15 to 35-year-old men with high incidence among all solid malignancies. Approximately 9,000-72,000 people die of testicular cancer every year [1]. Radical orchiectomy is used for both diagnostic and therapeutic purposes. After surgery, further treatment is determined based on histology, tumour invasion and other risk

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factors. In the 1970s, effective chemotherapy regimens led to a 64-95% increase in 5-year survival rates [2]. Cisplatin-based combination treatments offer a cure even for patients with extensive organ metastasis or poor prognostic tumour markers. These developments have made testicular cancer the solid organ malignancy with the highest chance of a cure [3].

Three to four cycles of bleomycin, etoposide, cisplatin-based treatments with or without retroperitoneal lymph node dissection offer a 41% chance of a cure in metastatic germ cell patients with poor prognostic factors and a 92% chance of a cure in patients with better prognostic factors [4]; 60% of patients with mild and poor risk factors may need additional treatments, which are determined by the patient's chemotherapy history, previous regimens and response to chemotherapy.

The likelihood of curing patients who relapse or are refractory is low, especially for platinum refractory disease, where most patients die after treatment failure in first-line chemotherapy. Due to the difficulty of achieving cures for chemotherapy-refractory cancers, previous studies have mostly focused on understanding the mechanisms underlying refractoriness and developing appropriate treatments. The simplest way to decrease refractoriness is by increasing the dose of chemotherapy [5]. In the 1980s, high-dose chemotherapy (HDCT), which had not been used previously due to haematological toxicity, became a therapeutic option and increased the ratios for survival and possible cures [6]. Salvage treatment in refractory patients with haematological stem cell supported HDCT, achieved mortality rates below 5% and DFS rates were between 40 and 70% [7-11].

Carboplatin and etoposide based HDCT was first used at Indiana University in 1986. The most pressing problem with HDCT was toxicity and related mortality; however, the availability of peripheral stem cell-supported HDCT since 1996 has shortened engraftment durations, reduced complications and increased the chance of cure, even for patients who had received regimens with two or more chemotherapy lines [7, 12]. To date, no randomized trial has been conducted to demonstrate the superiority of HDCT protocols used for ASCT. The present study aimed to compare two commonly used HDCT regimens for an extended period of time with real-life data.

Methods

Approval for the retrospective study was obtained from the ethics committee of Gülhane Training and Research Hospital. Fifty refractory testicular cancer patients over the age of 18 were treated with HDCT and ASCT at the hospital from January 2011 to July 2018. The variables evaluated were patient demographics; βhCG, AFP and LDH-included biochemical tests; location, histopathological types and T-stages of tumours; lymph node involvement; distant metastasis; orchiectomy condition; chemo- and radiotherapy history; relapse and refractory condition; time of ASCT and engraftment; type HDCT regimen; side effects; and survival with and without progression. Histopathological types were classified according to the WHO guidelines, and patients were staged according to the American Joint Committee on Cancer and the Union for International Cancer Control's guidelines. Information on patient survival was obtained from hospital charts and the deceased information system of the National Institute of Health.

All patients were diagnosed with refractory testicular cancer and received at least two lines of chemotherapy and three or four cycles of BEP (Bleomycin 30 mg/day at D1, D8 and D15; Etoposide 100 mg/m^2/day on D1 and D5; Cisplatin 20 mg/m^2/day at D1, D5 every 21 days). The most commonly applied salvage therapy was a TIP (Paclitaxel 175 mg/m^2/day D1; Ifosfamide 1,000 mg/m^2/day D1, D2 and D3; Mesna 1, 000 mg D1, D2 and D3; Cisplatin 60 mg/m^2/day D1 every 12 days). Stem cells were injected subcutaneously 10 μg/kg/day and granulocyte colony-stimulating factor (G-CSF) on the fifth day of therapy. Half of the patients received carboplatin and etoposide (CE) as their HDCT regimen, while the other half received ifosfamide, carboplatin and etoposide (ICE). The CE regimen protocol included 700mg/m^2 carboplatin combined with 750 mg/m^2 etoposide on days one to three and autologous stem cell reinfusion on day six [13]. For the ICE regimen, ifosfamide 12 g/m^2 (divided into one to six days), carboplatin 1,200 mg mg/m^2 (divided into one to six days) and etoposide 1,200 mg/m^2 (divided into one to six days) were used and autologous stem cell reinfusion on the eighth day [14].

After the autologous stem cells infusion, patients were treated with G-CSF. Thrombocyte engraftment was prescribed with thrombocytes higher than 20×10^9/l for three consecutive days, while neutrophil infusion was prescribed with neutrophil number ≥500×10^3/l. The primary goal of this therapy was to assess the patients' one-year PFS; the secondary goal was to identify clinical prognostic factors for disease progression after ASCT and to define the safety and the toxicity profile of both the HDCT and ASCT.

Statistics

Statistical analyses were performed using SPSS, version 18.0 for Windows (SPSS, Inc., Chicago, IL, USA). Descriptive statistics, standard deviation, and mean, minimum and maximum values were used for continuous (quantitative) variables, while categorical variables were expressed as numbers (n) and ratios (%). An independent t-test or one-way analysis of variance (ANOVA) were used to compare the groups, and x^2 test was used to determine group relations according to categorical variables. The statistical significance level in the calculations was set at 5%. PFS was defined as the time from diagnosis to progression, recurrence or death, while overall survival (OS) was the time from diagnosis to death.

Results

Fifty patients with metastatic refractory testicular carcinoma with a median age of 34 years were included in the study. Of these cases, 90% had stage III disease at the time of diagnosis. Thirty-six patients were diagnosed with mixed germ cell tumours (72%), two with choriocarcinoma (4%), four with embryonal carcinoma (8%), five with yolk sac tumours (10%) and three with seminoma (6%). All but eight (16%) patients were at high risk.

CE was used as salvage treatment for half of the patients and ICE was used for the other half. Four patients responded completely and 30 responded partially to ASCT. The clinical benefit ratio was calculated as 68%. Partial response rates were the same in both treatment groups but 3 of 4 cases with complete response were in the CE group.

After transplantation, progression was observed in 9 patients in the ICE group and in 6 the CE group. Two patients died due to ileus and bleeding in the early post-transplant period. Fifteen cases (30%) became refractory to ASCT and progressed.

Post-transplantation median PFS was calculated as 22 months (3-180). Although there was a trend in favor of ICE for progression-free survival, it did not reach statistical significance (p=0.06, Figure 1).

The median survival in the overall study population was 223.4 months (76.1-370.7). Although there was a difference in OS between chemotherapy groups, the difference was not statistically significant (p=0.06, Figure 2).

Mean engraftment time for the ASCT was 13.3 ± 3.1 days. The mean duration of engraftment in patients treated with CE was 11.2 ± 2.3 days, while it was 15.5±2.1 days in patients receiving ICE. This difference between the two treatment groups was statistically significant (p<0.001).

In terms of chemotherapy toxicity, neutropenia, thrombocytopenia and nausea were detected in both groups. Neuropathy was similar in both chemotherapy subgroups (68-80%, p=0.5). Similarly, no significant difference in ototoxicity, emesis, diarrhea and bleeding was found between the two treatment groups.

Discussion

Due to the rarity of prospective randomized clinical trials, the optimal treatment for refractory germ cell tumours remains uncertain. Our study aimed to evaluate the efficiency, survival and toxicities of two different HDCT for refractory germ cell cancer patients with ASCT.

Currently there are no existing guidelines for choosing HDCT and ASCT treatment regimens as the first salvage treatment option in patients with relapsed/refractory germ cell tumours. However, in patients with good ECOG performance status and favorable organ functions, this treatment is shown to be effective as second-line salvage therapy [15, 16]. Fifty eight percent of our patients received HDCT and ASCT as second-line salvage therapy in accordance with guidelines.

A meta-analysis conducted by Petrelli et al showed that the response rates to HDCT and ASCT were 62.4% (95% CI 55.7-69) [17]. In our clinical practice, response rates were 68%, which is in concordance with the studies of other authors. Comparable to the results from Moht et al retrospective analysis, who showed that IGCCC patients with mild and bad prognostic factors have a PR rate of 36%, we found that this rate was 30% [18].

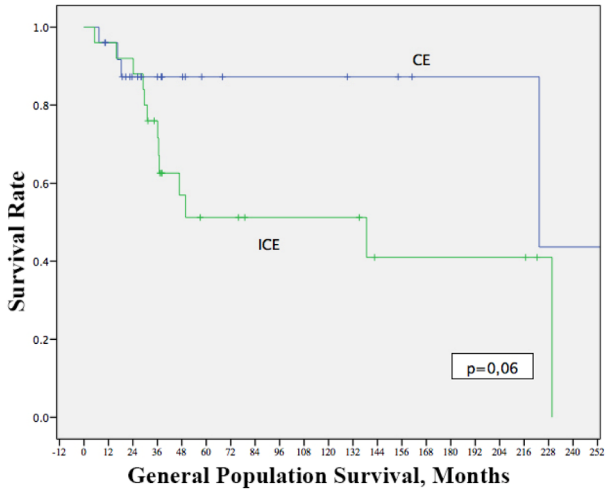

Figure 1. Overall survival in the two chemotherapy subgroups.

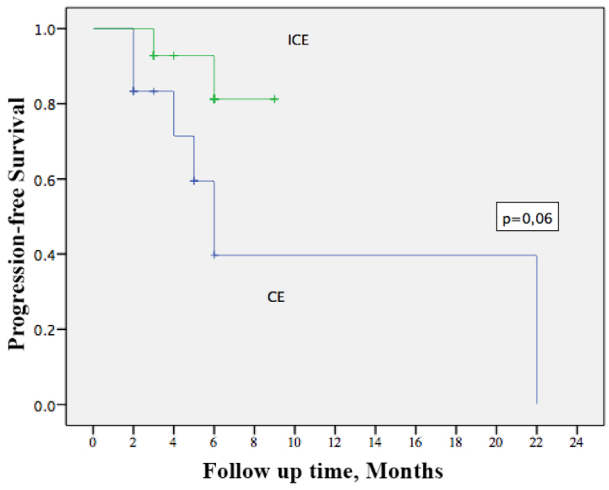

Figure 2. Progression-free survival in the two chemotherapy subgroups.

TAXIF II study by Selle et al demonstrated a mean PFS rate of 23 months [19]. Similarly, in our study we found a median PFS rate of 22 months. Between the ICE and CE groups there was a trend favoring ICE for PFS rate but this did not reach statistical significance (p=0.06).

Comparable to the previous study by Broun et al, where the mean engraftment time was 12±3 days [20], in our study it was 13.3±3.1 days. Mean engraftment time was 11.2 ±2.3 days in patients treated with CE and 15.5±2.1 days for the ICE group and these differences between the chemotherapy groups were statistically significant (p<0.001). This supports the effectiveness of this regimen as it reduces the duration of hospitalization.

Motzer et al used induction with paclitaxel and ifosfamide, and after high dose carboplatin/etoposide protocol (TI-CE), the 3-year follow-up OS rate was 54% [21]. Rick et al used 3 TIP courses and 1 course of HDCT and reported a 30% survival rate at 3-year follow up [22]. Two-year PFS and OS rates in patients getting only CE treatment was 60% and 66%, respectively. Durable disease control rates were 50% for the CE regimen used as third-salvage treatment [23]. In our study, median OS was calculated as 223.4 months (76.1-370.7). Although there was a difference in OS between chemotherapy groups, this difference was not significant (p=0.06).

Myelosuppression, otologic abnormalities, nausea, vomiting, peripheral neuropathy, dehydration, and mucositis are the primary toxic effects of HDCT [24]. Adra et al found 2.4% treatment-related mortality in ASCT [25], whereas it was 5.5% in the Hege et al study [26]. The most common cause of treatment-related mortality was infectious diseases. Similar to the results in the literature, we found 4% treatment-related mortality and the most common adverse reactions were neutropenia and thrombocytopenia.

There are some limitations in our study. First, our study consisted of rare cases who underwent ASCT due to relapsed or refractory GCT. As a result, our sample size was small. Second, our patient population was heterogeneous with respect to indications for ASCT, and the follow up times were relatively short. In addition, it was a retrospective study.

In conclusion, we found that for patients with relapsed/refractory germ cell tumour, high dose carboplatin/etoposide and high dose ifosfamide/carboplatin/etoposide regimens were both safe and effective. Although OS in the chemotherapy groups was different, this was not statistically significant. In the CE group the mean engraftment time was shorter than that of the ICE group. Furhtermore, both treatment regimens were associated with low treatment-related mortality. Future prospective randomized studies should continue to investigate effective survival outcomes in this subset of patients.

Conflict of interests

The authors declare no conflict of interests.

References

1. Global Burden of Disease Cancer Collaboration. Fitzmaurice C, Allen C, Barber RM et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncol 2017;3:524.
2. Einhorn LH. Treatment of testicular cancer: a new and improved model. J Clin Oncol 1990;8:1777.
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA: Cancer J Clin 2016;66:7-30.
4. Hinton S, Catalano PJ, Einhorn LH et al. Cisplatin, etoposide and either bleomycin or ifosfamide in the treatment of disseminated germ cell tumours: final analysis of an intergroup trial. Cancer 2003;97:1869.
5. Porrata LF, Adjei AA. The pharmacologic basis of high dose chemotherapy with haematopoietic stem cell support for solid tumours. Br J Cancer 2001;85:484-9.
6. 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 tumours. J Clin Oncol 2007;25:247.
7. Einhorn LH, Williams SD, Chamness A et al. High-dose chemotherapy and stem-cell rescue for metastatic germ-cell tumours. N Engl J Med 2007;357:47-51.
8. Bokemeyer C, Harstrick A, Beyer J et al. The use of dose-intensified chemotherapy in the treatment of metastatic nonseminomatous testicular germ cell tumours. German Testicular Cancer Study Group. Semin Oncol 1998;25:24.
9. Beyer J, Kingreen D, Krause M et al. Long-term survival of patients with recurrent or refractory germ cell tumours after high dose chemotherapy. Cancer 1997;79:161.
10. Beyer J, Stenning S, Gerl A et al. High-dose versus conventional-dose chemotherapy as first-salvage treatment in patients with non-seminomatous germ-cell tumours: a matched-pair analysis. Ann Oncol 2002;13:599.

11. Lorch A, Mollevi C, Kramar A et al. Conventional-dose versus high-dose chemotherapy in relapsed or refractory male germ-cell tumours. J Clin Oncol 2010;28:345s (abstr no.4513).
12. Feldman DR, Sheinfeld J, Bajorin DF et al. TI-CE high-dose chemotherapy for patients with previously treated germ cell tumours: results and prognostic factor analysis. J Clin Oncol 2010;28:1706-13.
13. Adra N, Abonour R, Althouse SK, Albany C, Hanna NH, Einhorn LH. High-dose chemotherapy and autologous peripheral-blood stem-cell transplantation for relapsed metastatic germ cell tumours: the Indiana University experience. J Clin Oncol 2017;35:1096-102.
14. Siegert W, Beyer J, Strohscheer I et al. High-dose treatment with carboplatin, etoposide, and ifosfamide followed by autologous stem-cell transplantation in relapsed or refractory germ cell cancer: a phase I/II study. The German Testicular Cancer Cooperative Study Group. J Clin Oncol 1994;12:1223-31.
15. Adra N, Althouse SK, Liu H et al. Prognostic factors in patients with poor-risk germ-cell tumours: a retrospective analysis of the Indiana University experience from 1990 to 2014. Ann Oncol 2016;27:875-9.
16. 16. 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 tumours. Ann Oncol 2010;21:820-5.
17. Petrelli F, Coinu A, Rosti G, Pedrazzoli G, Barni S. Salvage treatment for testicular cancer with standard- or high-dose chemotherapy: a systematic review of 59 studies. Med Oncol 2017;34:133.
18. Mohr M, Hartig I, Kessler T et al. High-dose chemotherapy with autologous PBSC transplantation for poor prognosis germ cell tumours: A retrospective monocenter analysis of 44 cases. Bone Marrow Transplant 2012;47:1321-5.
19. Selle F, Wittnebel S, Biron P et al. A phase II trial of high dose chemotherapy (HDCT) supported by hematopoietic stem-cell transplantation (HSCT) in germ-cell tumours (GCTs) patients failing cisplatin-based chemotherapy: the Multicentric TAXIF II study. Ann Oncol 2014;25:1775-82.
20. Broun ER, Hromas RA, Nichols OR et al. Tandem High Dose Chemotherapy with Autologous Bone Marrow Transplantation for Initial Relapse of Testicular Germ Cell Cancer. Cancer 1997;79:1605-10.
21. Motzer RJ, Mazumdar M, Sheinfeld J et al. Sequential dose-intensive paclitaxel, ifosfamide, carboplatin, and etoposide salvage therapy for germ cell tumour patients. J Clin Oncol 2000;18:1173-80.
22. Rick O, Bokemeyer C, Beyer J et al. Salvage treatment with paclitaxel, ifosfamide, and cisplatin plus high-dose carboplatin, etoposide, and thiotepa followed by autologous stem-cell rescue in patients with relapsed or refractory germ cell cancer. J Clin Oncol 2001;19:81-8.
23. Hamid AA, Markt SC, Vicier C et al. Autologous Stem-Cell Transplantation Outcomes for Relapsed Metastatic Germ-Cell Tumors in the Modern Era. Clin Genitourin Cancers 2018;17:58-64.
24. Bhatia S, Abonour R, Porcu P et al. High-dose chemotherapy as initial salvage chemotherapy in patients with relapsed testicular cancer. J Clin Oncol 2000;18:3346-51.
25. Adra N, Abonour R, Althouse SK, Albany C, Hanna NH, Einhorn LH. High-dose chemotherapy and autologous peripheral-blood stem-cell transplantation for relapsed metastatic germ cell tumours: The Indiana University Experience. J Clin Oncol 2017;35:1096-102.
26. Hege SH, Anna L, Ulrika S et al. High-dose chemotherapy with autologous stem cell support in patients with metastatic nonseminomatous testicular cancer - a report from the Swedish Norwegian Testicular Cancer Group (SWENOTECA). Acta Oncologica 2012;51;168-76.