ORIGINAL ARTICLE

Is there an intermediate-risk non-seminoma? Long-term treatment results from a single center

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Summary

Purpose: We retrospectively assessed the treatment results of patients with testicular non-seminoma to evaluate possible predictive and prognostic factors.

Methods: 189 patients with testicular non-seminoma treated between 2000 and 2012 were retrospectively evaluated. Treatment was based on orchiectomy plus chemotherapy (bleomycin/etoposide/cisplatin and vinblastine/ifosfamide/cisplatin); retroperitoneal lymphadenectomy was only performed for residual disease after chemotherapy. The treatment protocol was updated regularly according to international standards. Overall survival (OS) was evaluated with the Kaplan-Meier method at a significance level of 5% according to stage, Karnofsky performance status (KPS), and chemotherapy dose intensity.

Results: OS differed significantly for patients at different TNM stages (p=0.000); however, detailed analysis revealed significantly worse survival only in stage IIIC (10-year OS for IIIC vs IIIA+B, 35 vs 88%, p=0.001), while the difference between IIIB and lower stages was not significant (p=0.383). Patients with no chemotherapy dose reduction had significantly higher OS than those with any kind of dose reduction (10-year OS 96 vs 0%, p=0.000). For stage IIIC disease, however, dose intensity had no influence on OS (p=0.167). KPS had no prognostic significance for OS (KPS<80 vs ≥80, p=0.627) for stage IIIA+B and for stage IIIC.

Conclusion: The standard of care for testicular non-seminoma offers excellent prognosis with no significant differences in OS for good- and intermediate-risk patients. Reduction of chemotherapy dose negatively impacted OS in patients with stage IIIA+B and thus should be avoided.

Key words: chemotherapy, germ cell tumors, non-seminoma, testicular cancer

Introduction

Although germ cell tumors (GCTs) comprise only about 2% of all human malignancies, in the 15-to 34-year age group they are the most common malignant tumors in males [1]. The worldwide incidence of these tumors has doubled over the past 40 years. The incidence of GCTs in the Czech Republic ranked seventh in Europe in 2008 [2].

In 1997, the International Germ Cell Cancer Consensus Group (IGCCCG) defined a classification system based on the identification of several clinically independent prognostic features, such as disease extent and the levels of serum tumor markers. Post-orchiectomy tumor markers underlie IGCCCG risk classification, and divide groups the patients with pure seminoma and non-seminoma GCTs into good-, intermediate-, or poor-risk groups [3]. Post-orchiectomy treatment intensity is adapted to these categories.

Treatment of GCTs in the Czech Republic is centralized into a small number of specialized cancer centers. University Hospital Ostrava has a long tradition of treating these malignancies. In this article we present a retrospective analysis of the treatment results of non-seminoma GCTs, with a special focus on risk factors. The goal of our study was to determine whether IGCCCG criteria can be applied to a single-center cohort of patients with GCTs.

Methods

Between 2000 and 2012, 189 patients with testicular non-seminoma GCTs were treated at our center. The median patient age on presentation was 31 years (range 18-77). The treatment consisted of inguinal orchiectomy in all cases. Surveillance was recommended for patients with stage IA disease (22 cases); all other patients were treated with chemotherapy. Retroperitoneal lymphadenectomy was not performed as primary treatment. The chemotherapy regimen of choice was bleomycin/etoposide/platinum (BEP; Table 1).

In patients with negative tumor markers and post-chemotherapy residual infradiaphragmatic disease visible on computed tomography, surgical disease resection was performed (N=42). Following surgical resection, patients without viable tumor or with mature teratoma received no further treatement, while patients with residual viable (>10%) tumor (e.g., immature teratoma, embryonal carcinoma, yolk sac tumor, seminoma, or choriocarcinoma) were offered two additional cycles of chemotherapy (in case of R0 resection, etoposide/ifosfamide/cisplatin; in case of R1-2 resection, vinblastine/ifosfamide/cisplatin). Two to four cycles of further chemotherapy were also given to patients with partial or no response to first-line treatment. The regimen used for second-line treatment was vinblastine/ifosfamide/cisplatin as well.

Granulocyte colony-stimulating factor (G-CSF) was administered to selected patients to maintain proper chemotherapy dose intensity. It was given as primary prophylaxis in patients with considerable risk of neutropenia i.e. all patients treated with vinblastine/ifosfamide/cisplatin chemotherapy, patients with KPS <80%, and patients 40 years and older (N=51). In patients with grade IV neutropenia after the first cycle, G-CSF was given as secondary prophylaxis (N=78).

Statistics

OS was evaluated according to disease stage, KPS, and intensity of chemotherapy. For statistical analysis, IBM SPSS Statistics for Windows, version 16.0 (IBM, New York, NY) was used. OS was calculated from the date of diagnosis to December 31, 2012 using the Kaplan-Meier method with log rank test for estimating significant differences between groups. The level of significance was set at $p<0.05$ (two-sided p values).

Results

After a median follow-up of 68 months (range 6-154) 22/189 (12%) patients had died (13 patients with stage IIIC). In general, there was a highly significant difference in OS (log-rank, p=0.000) according to disease stage (Figure 1). However, this significance only pertained to stages I+II vs stage III; no significant difference in OS was found between stages I and II (log-rank, p=0.517).
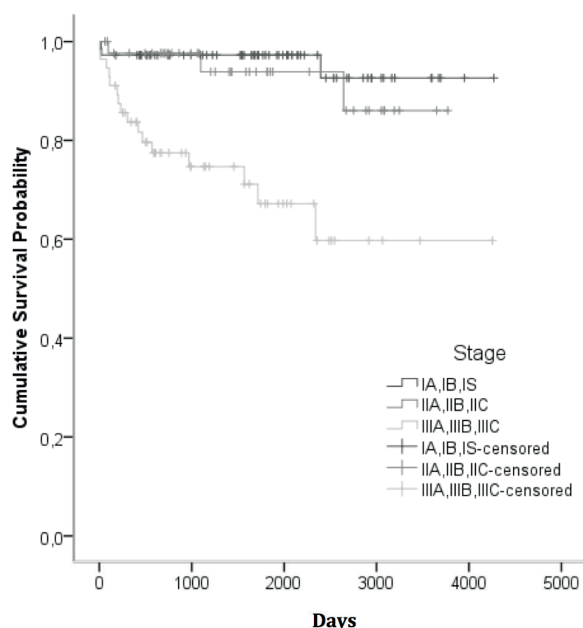
Figure 1. Overall survival according to stages I-III (log rank, p=0.000). Removing stage III results in log rank, p=0.517.

More detailed analysis of OS revealed that only patients with high-risk non-seminoma GCTs (stage IIIC) displayed worse prognosis compared to other patients. There was a highly significant difference in OS between stages I-IIIB and stage IIIC (log-rank, p=0.000), but no statistically significant difference was noted among stages I-IIIB (log-rank, p=0.383; Figure 2A) or between good and intermediate prognosis group (log-rank, p=0.093; Figure 2B).

Survival analysis of stage III patients confirmed the gap between stages IIIA+B and stage IIIC. Of the 31 patients in stages IIIA+B, 28 (90%) remain alive, while in the group of patients with stage IIIC disease there were 13 deaths (52%); 12 patients (48%) remain alive (Figure 3).

Since the treatment protocols were very homogeneous, we investigated several variables that might have contributed to the survival results. KPS was 80% or higher in 12 patients (48%) and lower than 80% in 13 patients (52%) with stage IIIC disease. However, KPS displayed no influence on survival in poor-risk patients (log-rank, p=0.08; Figure 4).

Further possible adverse prognostic factors were evaluated in patients with stage IIIC disease. There was no significant difference in the OS of patients with distant metastases other than lymph nodes or lung (M1b) compared with that of patients with very high levels of serum tumor markers (S3; log-rank, p=0.573). Also, reduction
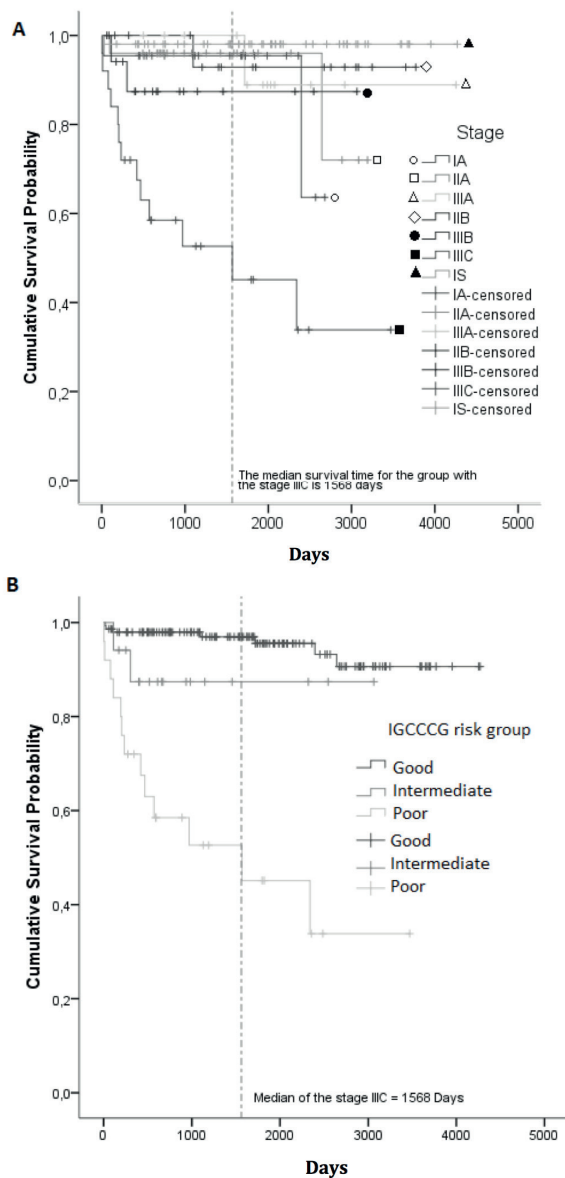
Figure 2. Detailed survival data according to disease stage **(A)** and prognostic group **(B)**. Stages IB and IIC were analyzed, but are not shown; these survival curves were identical to the clinical stage curve because there were no deaths. **A:** In general, significant differences existed in overall survival between the tested patients in terms of stage and IGCCCG risk group (log rank, p=0.000). Removing stage IIIC results in non significant difference (log rank, p=0.383).**B:** Significant difference in overall survival existed between intermediate and high risk groups (log rank, p=0.000), while such difference didn't exist between good and intermediate risk groups (log rank, p=0.093).

Figure 3. Overall survival in patients with stage III disease (log rank, p=0.001).

Figure 4. Overall survival according to Karnofsky performance status (KPS) in patients with high-risk (IIIC) non-seminoma (log rank, p=0.083).

in chemotherapy dose intensity, which had to be carried out in 4 patients with stage IIIC disease due to poor general medical condition, did not influence OS (dose reduction yes vs no, log-rank, p=0.167). On the other hand, chemotherapy dose intensity was a significant predictive factor for
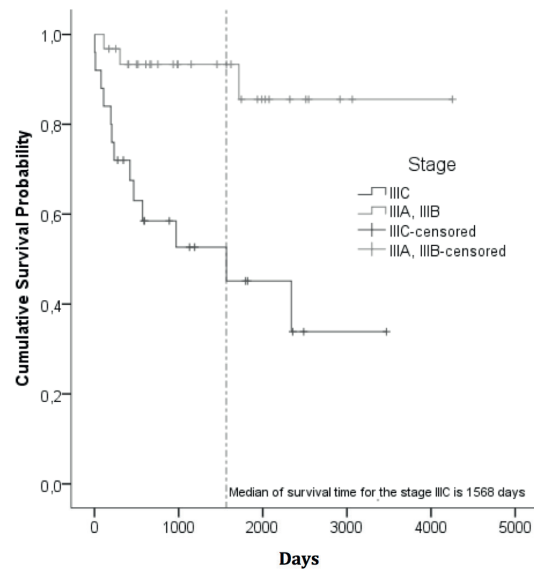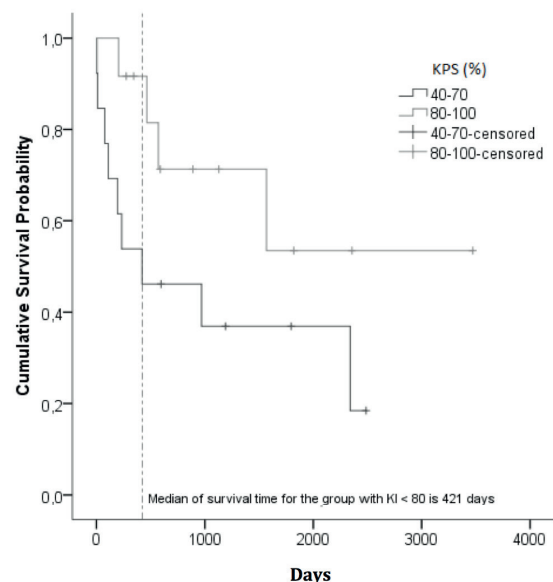
OS in patients with stage IIIA+B disease; patients with no dose reduction had a significantly higher OS than patients with any kind of dose reduction (10-year OS 96 vs 0%, log-rank, p=0.000).

Discussion

Although GCTs are uncommon, the worldwide incidence of this cancer is on the rise. With the advent of platinum-based chemotherapy, GCTs have become highly curable, even in advanced stages. A precise prognostic classification system is required to assist physicians in choosing the appro-

priate treatment for every patient.

There is more than one treatment option available for some stages of the disease. Our center's approach is to omit primary retroperitoneal lymph node dissection (RPLND) after orchiectomy, to focus on surveillance in stage IA, and to administer two or more cycles of chemotherapy in other stages. For stage IA, the cure rates of surveillance and RPLND are comparable [4,5]; for stage IB, there is strong evidence supporting the use of chemotherapy instead of lymphadenectomy [6-8]. A randomized study compared RPLND with one cycle of BEP and reported significantly fewer relapses after chemotherapy [9]. However, these results must be interpreted with caution because RPLND was unilateral, which is not a standard approach.

For more advanced stages, chemotherapy is undoubtedly the standard treatment option post-orchiectomy. Treatment should be tailored to the patient in order to maintain efficacy and reduce toxicity. Although three cycles of BEP can be substituted by four cycles of etoposide/platinum [10,11], our standard of care consists of the classical BEP regimen, which is more intense but has a shorter overall treatment time.

Looking at the results, one can assume that the IGCCCG risk groups do not completely match our survival data; our good- and intermediate-risk patients showed the same excellent prognosis, with 5-year OS around 90%. To the best of our knowledge, our group is the first to eliminate the difference in OS between these two risk groups while maintaining the excellent survival of the good-risk patients. Data published by other authors note clear differences in survival between good- and intermediate-risk patients. In the study of Bhala et al. [12], the 5-year OS rate of 178 patients with non-seminoma GCTs was similar to the data from the IGCCCG classification for the good-risk (95%) and intermediate-risk groups (82%), resulting in a difference of 13%. A Japanese study [13] of 74 non-seminoma cancer patients reported progression-free survival instead of OS, with a difference of 20% (90% and 70% for the good- and intermediate-risk groups, respectively, p=0.02). Perhaps the best survival results were published by Sonneveld et al. [14]; the 10-year OS rates for the good- and intermediate-risk groups were 94% and 87%, respectively. This difference was statistically significant, indicating that a difference between the risk groups remained.

The dose intensity of BEP may have influenced our results, as it was a significant predictive factor for relapse and survival in our analysis. In general, there are very few reports in the literature that consider this topic. Dose intensity is mainly addressed to poor-risk patients, but with no or minimal impact on survival [15-17]. Some studies have included good-risk non-seminoma patients as well, but given the excellent prognosis of these patients, these investigations have focused on toxicity reduction; dose intensity was not an issue in these studies [18,19]. In the intermediate-risk group, there is evidence that bleomycin should not be replaced by ifosfamide [20], but the impact of proper dose intensity on the survival in intermediate-risk non-seminoma patients has not yet been published.

A second possible reason for our survival results may be the size of our center, which is among the two largest centers in the Czech Republic. There is some evidence that high-volume centers achieve better-than-average results. Feuer et al. [21] compared survival data from patients treated at Memorial Sloan-Kettering Cancer Center in New York City, USA, to data in population-based registries of the Surveillance, Epidemiology, and End Results (SEER) program; survival in the former dataset was significantly better than in the latter dataset for minimal/moderate disease (95% and 73% 3-year overall survival rates, respectively). However, the difference for advanced cases was only marginally significant (52% and 40% 3-year survival rates, respectively). In a Norwegian trial [22], the volume of the center was also a significant prognostic factor that favored large oncology units, but unlike the previous study this trend was valid for both early and advanced stages of GCTs. Analyzing patients from specialized centers only may introduce a referral bias, since perhaps only a certain subset of patients, such as those perceived to have the worst prognosis, may have been referred. In addition, much of the data come from patients who participated in clinical trials, which may also influence the outcome compared with a general population of treated patients. It seems as if the IGCCCG prognostic system is better suited to a population-based cohort with a similar distribution of categories and clear prognostic ability.

Conclusion

The standard of care for testicular non-seminoma GCTs offers excellent prognosis with no significant differences in OS for good- and intermediate-risk patients. Reduction of the chemotherapy dose intensity negatively impacts OS in patients with stage IIIA+B tumors, and therefore it should

be avoided. KPS does not exert any impact on OS for stages IIIA+B and for stage IIIC tumors. Outcomes for stage IIIC cancers are relatively poor, and thus further research on this topic is highly desirable.

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