The treatment of stage A testicular seminoma by carboplatin monochemotherapy

Lečenje seminomskih tumora testisa u stadijumu A monohemioterapijom karboplatinom

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Abstract

Background/Aim. Although radiotherapy is considered to be a standard treatment of stage A testicular seminoma, an increasing number of studies have reported encouraging results of the treatment by carboplatin monotherapy (CBDCA). The aim of this study was to analyse the treatment results of patients with clinical stage A seminoma treated by CBDCA on daily basis in the period June 1999 to September 2008. Methods. A total of 124 patients, mean age 36.63 years (20–62 years), with stage A testicular seminoma were treated, upon radical orchietomy, by adjuvant CBDCA (400 mg/m² on day 1 and 22). Results. Chemotherapy was well tolerated, except moderate nausea on the day of the drug administration and the following day. No patient had any serious disorders in blood cells count requiring substitutional treatment. During the mean follow-up period of 37.5 (range 6–111) months, three relapses were noted (2.41%) and none neoplasm of contralateral testicle or any other organ. Conclusion. Simple and easy carboplatin administration with excellent treatment results, along with good tolerance and absence of comorbidity, poses itself as a new “gold standard” of treatment for stage A testicular seminoma.

Key words: seminoma; drug therapy; carboplatin; orchiektomy; prognosis.

Introduction

Standard treatment of clinical stage A testicular seminoma includes radical orchietomy and adjuvant radiotherapy of ipsilateral pelvic and paraaortic lymph nodes. This treatment has been applied in the past 50 years, and yielded excellent results with low recurrence rate (2–5%), and ex-
tive to radiotherapy was surveillance, resulting in a rather high relapse rate (15–25%), increased morbidity, related to additional cisplatin chemotherapy followed by nephrotoxicity, ototoxicity, neurotoxicity and marked nausea and vomiting.

Given that seminomas are chemosensitive and radioresistant, a new option has emerged – carboplatin. Carboplatin is less toxic than cisplatin analogues, which appeared to be effective for the treatment of advanced seminomas. Carboplatin monotherapy proved to be highly efficient for eradication of micrometastatic disease. The results of recently published studies proved almost hundred percent of effectiveness, and in comparison with other therapies, this mode of treatment posed itself as the most effective. However, it has to be taken into account that all the published results have been based on studies with relatively short follow-up period. Nevertheless, the latest results are promising.

We presented the treatment results of patients with stage A testicular seminoma treated with two cycles of carboplatin and the mean follow-up period of 37.5 months.

Methods

The patients with clinical stage A, histologically verified pT1, pT2 and pT3 testicular seminoma, and negative surgical section margins following the radical orchiectomy were included in the study. Clinical stage was determined according to physical examination, blood cells count and serum biochemical analysis, tumor markers (AFP, βhCG) levels before surgical intervention and on 7th postoperative day. Also, ultrasonography of the testicles and abdomen, computerized tomography (CT) of the abdomen and pelvis and chest radiography were performed. All the patients had normal AFP values (elevated AFP values excluded the patients from the study). Seventeen patients had elevated βhCG, normalizing following radical orchiectomy. A total of 124 patients with clinical stage A testicular seminoma were treated in the period June 1999 – September 2008. Approximately two weeks after the orchiectomy, on an outpatient basis, carboplatin was administered iv in the dose of 400 mg/m² with hydration before and after the infusion in a total period of 150 minutes, along with antiemetics (ondansetron 2 × 8 mg). Chemotherapy was given in two cycles every 21st day. Complete blood cells count analysis was performed every 7 days.

During the first year of follow-up, monthly determination of tumor markers (AFP, βhCG) and ultrasound of the abdomen and contralateral testicle were performed, while chest radiography was performed in three-month intervals. Computerized tomography of the abdomen and pelvis was done once per year. In the second year, the examinations were performed in a two-month intervals (tumor markers, ultrasound, chest radiography every 6 months); in year 3, the patients were examined on a 4-month basis (tumor markers, ultrasound, chest radiography every 6 months). After that the control exams were performed every 6 months until the fifth year. Until now, all the patients presented with normal findings.

Results

In the period June 1999 to September 2008, 124 patients were treated for clinical stage A seminoma of testicles. Mean age of the patients was 36.65 years, the youngest being 20 and the oldest 62 years. Out of them, 29 patients were younger than 30 years of age and 95 patients were over 30 years (Table 1).

![Table 1](image)

The left testicular tumor was found in 57 patients (45.96%), while tumor of the right testicle was recorded in 67 patients (54.04%). There were 25 cases with histological stage pT1, 79 with pT2 and 20 patients with pT3.

All 124 patients were treated with two cycles of carboplatin chemotherapy. All the patients had normal AFP values before and after the orchiectomy and 17 patients had elevated βhCG normalizing following radical orchiectomy. The therapy was well tolerated by all the patients except for mild nausea (16%) and vomiting (6%) (WHO grade 1). Along with the therapy, an antiemetic (ondansetron 2 × 8 mg) was administered. The therapy with the antiemetic continued for the next two post-treatment days.

Leukocytopenia grade 1 was reported in seven patients, while thrombocytopenia was noted in two of them. There were no episodes of febrile neutropenia. No delayed therapy for any reason was needed in any of these patients.

Three recurrences (2.41%) were reported in the mean follow-up period of 37.5 months (range 6–108). The first, 4 months after the therapy only with elevation of βhCG to 360, the second, 12 months after the therapy with relapse in the retroperitoneal lymph nodes (stage B3) and elevation of βhCG to 68, and the third, 30 months after the therapy with relapse in the retroperitoneal lymph nodes (stage B3). These three patients were treated with 4 cycles of PE protocol (cisplatin and etoposide) and complete remission was obtained. They were in the follow-up period for 20, 24 and 10 months, respectively. Fifty-six patients were followed-up for three or more years, among them 23 patients for more than five years (Table 2).

Out of 124 patients, 72 fathered children before the onset of treatment, 43 patients were single, six patients presented to andrologic clinic for the impaired sperm count parameters and infertility, and five fathered children after the therapy was completed (12 months after the completion in all five patients).

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Discussion

Testicular tumors are among the most curable neoplasms. Seminomas account for almost half of all testicular tumors, out of which ¾ are in clinical stage A. A total cure of testicular seminomas is achieved in over 95% [1,2]. Until cisplatin and carboplatin were introduced in the therapy, a standard treatment of stage A testicular seminomas was radical orchectomy and adjuvant radiotherapy, without any controversies. However, perennial follow-up of patients treated by conventional radiotherapy revealed late side effects, first of all, to gastrointestinal system, as well as development of secondary malignancy in a high proportion of patients [3]. Some authors, in search for solution, reduce radiation dose or narrow radiation field with satisfactory effect [4]. On the other hand, it is apparent that radiotherapy itself is over treatment for some patients, with potentially unnecessary late effect of radiation.

Due to above-mentioned facts, a new treatment option has arisen that will be equally successful with less toxic effects and less impact on patients daily activities. Surveillance as one of treatment options after radical orchectomy was a good choice regarding the reduction of complications and side effects of radiotherapy. However, the consequence was high percentage of recurrence (even 33% as reported by some studies) [5,6,7]. In the follow-up period of testicular seminomas, tumor markers (AFP, βhCG) are highly unreliable [8]. Relapse of tumors are usually detected by imaging techniques (ultrasound, CT), requiring regular control exams. Although the recurrence is successfully treated by combined cisplatin chemotherapy followed by high complete cure rate, toxicity of therapy and the need for retroperitoneal lymphadenectomy increase the morbidity and mortality.

Oliver et al. [9] first published the treatment results of clinical stage A testicular seminoma, by adjuvant monochemotherapy with two carboplatin cycles. After 16-month follow-up, one recurrence was reported. Dieckmann et al. [10] reported, in their study of 82 patients who had received 2 carboplatin cycles, no recurrence after monitoring of 16 months, as well as Krege et al. [11] who followed 43 patients 28 months. Nost et al. [12] monitored 36 patients during 52 months and reported no recurrence. In two largest published series, Reiter et al. [13] reported no recurrence in 107 patients followed-up approximately 74 months after the administration of 2 carboplatin cycles, and Steiner et al. [14] described two recurrences among 108 patients during mean follow-up period of 59.8 months. Dieckman et al. [15], comparing the effectiveness of one and two carboplatin cycles, noted that there were no recurrence in the group of 32 patients that received 2 cycles, while there was 8.6% of recurrence in the group of 93 patients that had only one cycle (average follow-up period of 48 months). Aparicio et al. [16] reported 2 recurrences in 60 patients treated by two Carboplatin cycles during follow-up of 52 months. In their latest series, Oliver et al. [17] treated 560 patients with one carboplatin cycle, and they reported 4.8% of recurring diseases during a 48-month follow-up period, that was almost equal (5.2%) to series of 885 patients treated with radiotherapy.

We analyzed 124 patients cured by 2 cycles of carboplatin (400 mg/m², on the 1st and 21st day). In the mean follow-up period of 37.5 (range 6–111) months, only three recurrences were recorded (2.41%), confirming the effectiveness of two carboplatin cycles for clinical stage A testicular seminoma.

Toxicity profile was presented in mild nausea and vomiting, as well as leukopenia. Drug concentration in a dose of 400 mg/m² was sufficient and did not require to be increased or corrected, according to AUC curve allowing application of a higher drug dose. The drug administration interval every 21 days was associated with no side effects that would require delay of therapy which was comparable with the observation of other authors [18,19].

Out of 19 married patients without children before the therapy, seven had no problem having a baby 12 months after the completion of the therapy, while six have presented to andrologic clinic for treatment of the impaired sperm count parameters (mild oligoasthenospermia).

Conclusion

Reviewing the literature data and our experience with administration of two carboplatin cycles as adjuvant monotherapy in patients with clinical stage A testicular seminoma, we believe that two cycles in a dose of 400 mg/m² administered every 21 days are an excellent treatment option. The effectiveness of the therapy, absence of significant toxic effects as well as good tolerance of therapy are the major qualities of a such treatment option. The necessity of long-term follow-up of these patients is significant for evaluation of probable late toxic effects of treatment, although, if any, they are expected to be minimal, affecting the fertility of patients and overall survival.

References


The paper received on September 29, 2008.