CASE REPORT

INDONESIAN JOURNAL OF CANCER

Paclitaxel, Iphospamide, and Cisplatin (TIP) as Bleomycin, Etoposide, and Cisplatin (BEP) Alternative for First-Line Therapy of Metastatic Germ Cell Tumor (GCT): A Case Series

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ARTICLE INFO

Received : 24 June 2019
Reviewed : 28 June 2019
Accepted : 27 September 2019

Keywords:
metastatic germ cell tumor, chemotherapy, testicular cancer

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ABSTRACT

Background: Bleomycin, etoposide, and cisplatin (BEP) is a standard first-line therapy for metastatic germ cell tumor (GCT), while paclitaxel, ifosfamide, and cisplatin (TIP) are commonly used as salvage therapy after failed BEP treatment. The unavailability of first-line drugs can be the reason for the use of second-line therapy. In this paper, we reviewed two initial cases of patients with metastatic GCT treated with TIP as first-line chemotherapy in our center.

Case Presentation: We reviewed the medical record and followed up two patients who had been treated with TIP as first-line chemotherapy for metastatic GCT due to lack of BEP regiment. We evaluated efficacy and toxicity of this treatment. These two patients were diagnosed with seminoma, with intermediate-risk according to International Germ Cell Cancer Collaborative Group (IGCCCG) classification. Both achieved complete response after four courses of TIP chemotherapy with toxicities mainly consisted of myelosuppression.

Conclusions: TIP demonstrated efficacy serves as the first-line therapy for germ cell tumors with an acceptable safety profile. Further studies with larger subjects are still needed for evaluation. However, TIP is more expensive compared to BEP, making BEP is still superior to TIP in public hospital setting where cost-effectiveness of treatment is important.

INTRODUCTION

Germ cell tumor (GCT) is a relatively rare disease, accounting for only 1% of all malignancies in men [1,2]. However, it still represents the most common solid tumor in men between 15 and 35 years of age [3]. There has been a marked increase in the incidence of testicular cancer worldwide [4]. In contrast to the incidence, there has been a remarkable decline in testicular cancer mortality over the past 30 years. Untreated testicular cancer may metastasize and eventually lead to death, but advances in treatment have resulted in increases in 5-year survival rates from 63 % to more than 90% during the last 3 decades [5,6]. The introduction of cisplatin-based chemotherapy regimens has resulted in the conversion of metastatic GCTs with an extremely poor prognosis into a curable solid malignancy. Among several regimes available, BEP, which consists of bleomycin, etoposide, and cisplatin, has proved to be highly efficacious against metastatic GCTs and is currently the most widely used regimen as the first-line therapy for metastatic GCTs [7].

However, the likelihood of sensitivity to chemotherapy and cure varies significantly on the basis of clinical and pathologic factors, which have been incorporated into the International Germ Cell Cancer Collaborative Group (IGCCCG) prognostic model. Although good-risk patients in this model have an approximately 90% progression-free survival (PFS) rate after chemotherapy, the corresponding rates for intermediate-risk and poor-risk patients are only 70% to 75% and 45% to 55%, respectively [8].

The combination of paclitaxel, ifosfamide, and cisplatin (TIP) was previously evaluated as a second-line treatment in phase I/II study of patients with testicular primary GCTs who relapsed after a favorable response to first-line chemotherapy. This regiment is also currently evaluated as the first-line therapy for metastatic GCT with intermediate and poor risks according to IGCCCG classification with satisfying results [9]. The unavailability of first-line drugs can be the reason for the use of second-line therapy as we know delayed management of metastatic cancer will increase progressivity and decrease overall survival._

At our institution, BEP was also the first-line chemotherapy to treat patients with metastatic GCTs until recent events where etoposide as the main component isn't available at our center due to several reasons. As a replacement, we treated patients with metastatic GCTs with TIP regiment based on several

previous studies. In this paper, we reviewed two initial cases of patients with metastatic GCT treated with TIP regiment as first-line therapy in our center due to lack of BEP regiment.

CASE PRESENTATION

During the last six months, there have been 2 patients with metastatic GCTs treated with TIP. We reviewed each case in this paper. We followed up each case during chemotherapy and evaluated the chemotherapy response and toxicity to each patient.

The TIP regiment consisted of paclitaxel 250 mg/m2 by 24-h infusion on day 1, followed by ifosfamide 1.5 g/m2 infusion over 2 hours and cisplatin 25 mg/m2 given over 2 hours on days 2–5. The dosages and schedule for cisplatin and ifosfamide administration were identical to the TIP regimen reported by The National Comprehensive Cancer Network (NCCN) Guidelines on testicular cancer. Mesna 500 mg/m 2 was administered intravenously before ifosfamide infusions and every 4 hours for a total of three doses per day Courses were repeated every 21 days.[10] All patients received prophylactic premedication with 20 mg dexamethasone 12 and 6 hours before paclitaxel and intravenous ranitidine and oral diphenhydramine (each 50 mg) 30 min prior to paclitaxel administrations, as a standard chemo protocol in our hospital. Standard anti-emetic and hydration protocols were followed.

Table 1. TIP chemotherapy regimen used in this case series compared to standard BEP regimen

TIP course	BEP course
Paclitaxel 250 mg/m2 IV on day-1 Ifosfamide 1500 mg/m2 IV on days 2–5 Mesna 500 mg/m2 IV before ifosfamide, and then 4 and 8 hours after each ifosfamide dose on days 2–5 Cisplatin 25 mg/m2 IV on days 2–5 Repeat every 21 days	Etoposide 100 mg/m2 IV on days 1–5 Cisplatin 20 mg/m2 IV on days 1–5 Bleomycin 30 Units IV weekly on Days 1,8, and 15 Repeat every 21 days

We evaluated chemotherapy response with the blood tumor marker and computed tomography (CT) scan following the complete course of chemotherapy. A complete response (CR) to chemotherapy alone was defined as marker normalization and radiographic resolution or marker normalization plus surgery revealing only necrosis or teratoma (no viable GCT). A CR to chemotherapy plus surgery is defined as marker normalization and complete surgical resection revealing viable GCT with negative margins. A partial response with negative tumor markers (PR-negative) is defined as marker normalization with residual radiographic abnormalities but without progression. The CR and PR-negative were considered favorable responses and required confirmation at 4 weeks or later by tumor markers and chest x-ray. An incomplete response (IR) was anything other than CR or PR-negative [11].

Toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Grade refers to the severity of the adverse events based on the general guideline as follows in **Table 2** [12]. After at least one dose of chemotherapy, the patient was eligible for toxicity assessment.

Table 2. Grading of chemotherapy adverse events according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Grade	Description
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local or noninvasive intervention indicated; limiting the age-appropriate instrumental activity of daily living
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activity of daily living.
4	Life-threatening consequences; urgent intervention indicated.
5	Death related to adverse events.

Case 1

The first case was a forty-one-year-old male, with the primary tumor on the left testicle. Preoperatively, the primary tumor was already spread to multiple lymph nodes in his left inguinal and paraaortic region. From pathological examination after left orchidectomy, it was testicular seminoma. After surgery, LDH and B-hCG were still elevated. He underwent TIP regiments for 4 cycles during 4 months. After the first chemotherapy cycle, the patient was admitted to the hospital with the low levels of hemoglobin (5.6 g/dL), leucocyte (1,200/ul), and thrombocyte (57,000/ul), each of which needed transfusion (Grade 3). This patient had been treated in the hospital for 2 weeks. Cycles 2 to 4 of chemotherapy passed without severe adverse events, and upon follow

up after courses he had complete chemotherapy response, with all tumor marker level normalized and no lymph node enlargement in follow up CT (**Figure 1**). Another nonhematologic adverse event experienced by this patient included nausea and vomitus (Grade 2).

Case 2

A forty-three-year-old male came with intraabdominal tumor. Upon history taking and physical examination, we found out that he didn't have intrascrotal left testicle since birth. Intraoperatively, the intraabdominal mass was removed. However, there were still parts of the tumor that can't be dissected. Pathological examination confirmed that the intraabdominal tumor was actually a GCT; seminoma, specifically. This patient underwent four cycles of TIP chemotherapy due to residual mass, paraaortic and inguinal lymph node enlargement, and elevated LDH and B-hCG. During the third chemotherapy cycle, the patient experienced anemia (7.7g/dL) and thrombocytopenia (89,000/ul), both requiring transfusion (Grade 3). This adverse event didn't happen in the first, second, and last chemotherapy cycles. We reassessed the patient following treatment, and both tumor markers had already been at the normal level and no apparent tumor mass from the CT (**Figure 2**).

DISCUSSION

Standard first-line chemotherapy regimens of GCT consist of BEP or without bleomycin (EP). However, the likelihood of sensitivity to chemotherapy and cure varies significantly on the basis of clinical and pathologic factors. According to IGCCCG prognostic model, good-risk patients have an approximately 90% PFS rate after chemotherapy, the corresponding rates for intermediate-risk and poor-risk patients are only 70% to 75% and 45% to 55%, respectively [9].

Meanwhile, the TIP regiment was originally developed as first-line salvage chemotherapy for testicular germ cell cancer patients who relapsed after the complete response (CR) or partial response (PR) with tumor marker-negative findings (PRm −) to prior chemotherapy [13,14]. As for TIP therapy following BEP failure as 2nd line therapy, Mead et al. [16] reported that the response rate was 38% and long-term disease-free survival was shown in 60% of cases.

In this paper, we reviewed TIP efficacy and toxicity as first-line chemotherapy for metastatic germ cell tumors as lack of BEP regimen in our center, especially for etoposide. Both of our cases were seminoma with intermediate-risk according to IGCCCG classification and both cases achieved complete response with chemotherapy alone. This result in line with Feldman et al, which reported 61% complete response for the intermediate-risk group, and 66% for the poor-risk group in response of TIP regiment as first-line therapy for germ cell tumor. Feldman et al also found that 94% patients with intermediate-risk achieve favorable response, compared to 74% patients of the poor-risk group [11].

Toxicities of TIP consisted mainly of myelosuppression and sensory neuropathy [15–17]. Both patients in this paper experienced Grade 3 of either anemia, leukocytopenia, or thrombocytopenia requiring a blood transfusion, support with granulocyte colony-stimulating factor and treated as inpatient. Nonhematologic toxicities experienced by these two patients are nausea and vomiting. No other treatment side effect reported, and more importantly, no death-related with treatment reported.

According to these two cases, TIP is a safe and effective first-line therapy for metastatic germ cell tumors. However, we assessed both treatment costs and it appears that with the same duration and course of treatment, TIP were roughly seven times more expensive than BEP. With a national healthcare system currently applied at our hospital, more expensive treatment will be more difficult to insurance covered, thus it would still be more convenient to use BEP as a primary treatment.

CONCLUSIONS

TIP demonstrated efficacy as first-line therapy for germ cell tumors with an acceptable safety profile as an alternative to standard BEP regiment. Further study with a larger sample is needed to evaluate this, and if needed, compare TIP with BEP head to head in term of efficacy and tolerability. However, TIP is far more expensive compared to BEP, making BEP is still superior to TIP in hospital setting where cost-effectiveness of treatment is important.

DECLARATIONS

Competing of Interest

There is no conflict of interest in this study.

Acknowledgment

No acknowledgment statement for this study

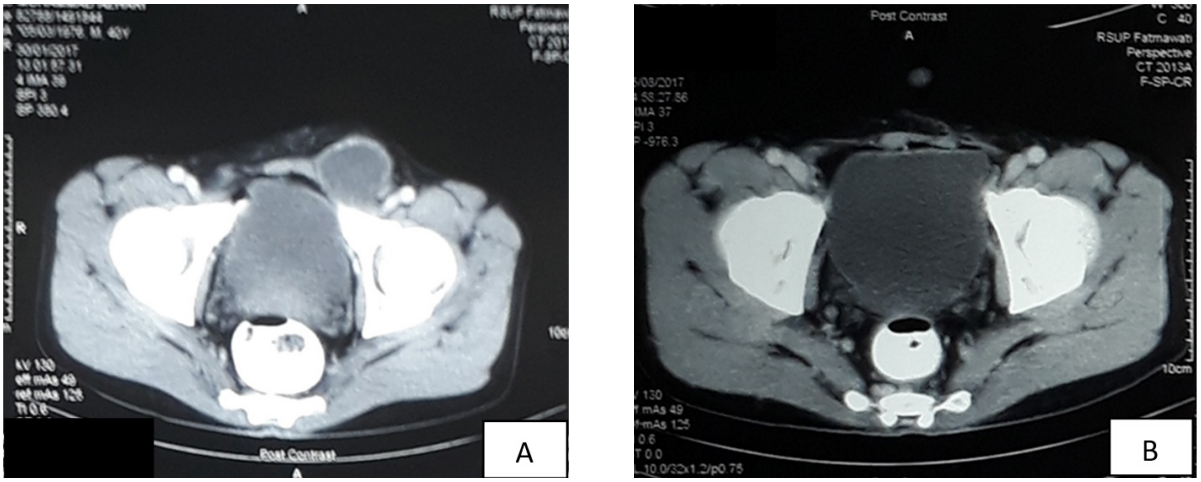

Figure 1. Left inguinal mass before (a) and after (b) four-course of chemotherapy.

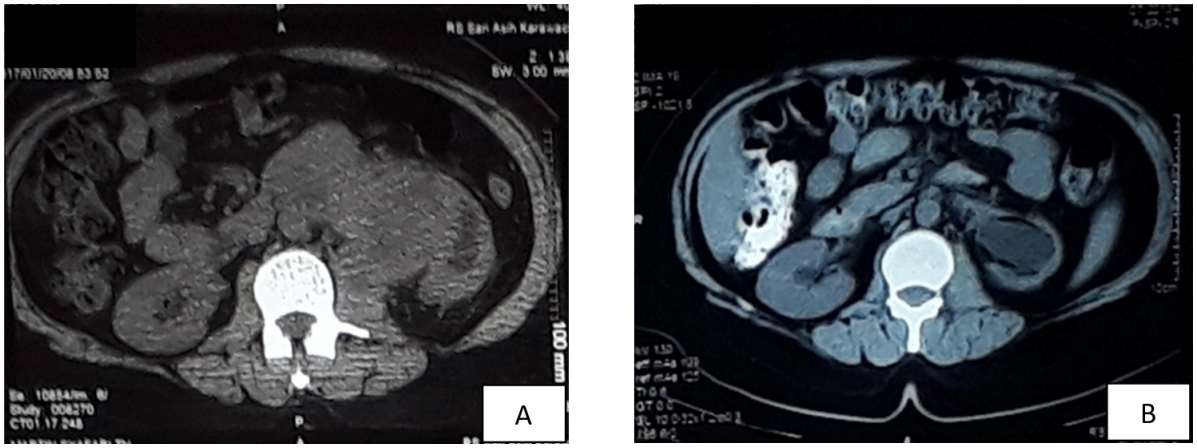

Figure 2. Intraabdominal mass before (A) and after (B) four-course of chemotherapy

Table 3. Summary of two cases

Characteristics	Case 1	Case 2
Age	41 yo	43 yo
Primary site	Left testicle	Intraabdominal (undescended testicle)
Pathology	Seminoma	Seminoma
AFP before chemotherapy	2.7 (N)	3.5 (N)
B-hCG before chemotherapy	94 (↑)	14.8 (↑)
LDH before chemotherapy	1968 (↑)	623 (↑)
CT scan features before chemotherapy	Dense mass on the left scrotal area expanding to left inguinal, multiple paraaortal lymphadenopathy	Multiple lymphadenopathies on the left inguinal, parailiac, and paraaortal region
IGCCCG Classification	Intermediate risk	Intermediate risk
Number of cycles	4	4
Adverse events	Anemia, leucocytopenia, thrombocytopenia, vomitus	Anemia, thrombocytopenia
AFP after chemotherapy	12.7 (N)	6.4 (N)
B-hCG after chemotherapy	2.5 (N)	< 1.2 (N)
LDH after chemotherapy	239 (N)	273 (N)
CT scan features after chemotherapy	Shrinkage of paraaortal lymph node (size < 0.5 cm), no visible tumor mass	Shrinkage of paraaortal ymphadenopathy, no visible other lymph nodes.

*AFP, alpha-fetoprotein; LDH, lactate dehydrogenase; B-hCG, beta-human chorionic gonadotropin; IGCCCG, International Germ Cell Cancer Collaborative Group; CT, computed tomography

P-ISSN: 1978-3744 E-ISSN: 2355-6811

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