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Risk analysis of subsequent therapies after first-line chemotherapy in advanced testicular cancer patients

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Abstract

Background: Testicular cancer is the most common solid cancer diagnosed among young men. Despite good response to chemotherapy and a high survival rate, subsequent salvage therapies may still be required for some patients in advanced stages. The predictive and prognostic markers are crucial unmet needs.

Methods: We retrospectively analyzed advanced testicular cancer patients who had received first-line chemotherapy between January 2002 and December 2020. The associations between baseline characteristics and clinical outcomes were evaluated.

Results: Of the 68 included patients, the median age was 29 years. Among them, 40 patients received only first-line chemotherapy while the remaining 28 received subsequent chemotherapy or surgeries. Data reveal that 82.5% (33/40) of the patients in the chemotherapy-only group were recorded as a good prognostic risk using the International Germ Cell Cancer Collaborative Group classification when compared with 35.7% (10/28) in the second-line therapy group. In the chemotherapy-only group, 53.8% of patients were presented with lymph node metastasis compared with 78.6% in the second-line therapy group ($p = 0.068$). Fifteen percent of patients (6/40) were recorded as S stage 2–3 in the chemotherapy-only group, whereas 85.2% (23/28) were recorded as such in the second-line therapy group ($p < 0.001$). The 5-year overall survival estimation was 92.9% in the chemotherapy-only group and 77.3% in the second-line therapy group. Univariate analysis for overall survival revealed that those patients at the S 2–3 stage and those receiving second-line therapies showed a trend of having an increased death risk (hazard ratio [HR] = 8.26, 95% confidence interval (CI), 0.99-68.67, $p = 0.051$; HR = 7.76, 95% CI, 0.93-64.99, $p = 0.059$, respectively). The S 2–3 stage was also independently associated with the risk of subsequent therapy (HR = 33.13; 95% CI, 2.55-430.64, $p = 0.007$).

Conclusion: Our real-world data show the predictive role of serum tumor marker stage 2–3 to be associated with any subsequent therapies after first-line chemotherapy. This can facilitate clinical decision making during the testicular cancer treatment process.

Keywords: Cisplatin; Non-seminomatous Germ Cell Tumor; Retroperitoneal Lymph Node Dissection; Seminoma

1. INTRODUCTION

Testicular cancer is the most common malignant solid tumor cancer seen among young men. According to the Cancer Registry Annual Report 2019 in Taiwan, the incidence of testicular cancer was 2.42 per 100 000 men, and accounted for 0.23% of the entire cancer subjects that year. Additionally, this rare cancer revealed its specificity in its low death rate, with only 0.14 per 100 000 men in 2019 dying from the disease. Germ cell tumors account for 95% of all testicular cancer cases comprising different histology types, including seminoma, embryonal cell carcinoma, yolk sac tumor, choriocarcinoma, and teratoma. Sex cord-stromal cell cancer is the other differentiation seen in testicular cancer and is usually excluded in clinical studies. Seminoma is the most common histological type of testicular cancer with an approximate 99% cancer-specific survival rate seen in stage 1 diseases. Other nonseminomatous germ cell tumors (NSGCT) have a more aggressive tumor nature, although the disease cure rate can still can reach as high as 70% to 90%.[1]

Despite the 99% estimated overall survival rate, patients will experience at least a 2% to 20% relapse rate even in stage I seminoma cancer with or without adjuvant therapy.[2]

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According to the International Germ Cell Cancer Collaborative Group (IGCCCG) risk classification, first-line systemic chemotherapy is recommended in NSGCT but remains controversial in seminoma.[3] Subsequent retroperitoneal lymph node dissection (RPLND) or metastasectomy is still an important tool for metastatic or relapse diseases.[4,5] Currently, clinical outcome prediction is crucial for the young men diagnosed with the disease during the period of treatment decision making. Hence, we retrospectively collected our testicular cancer patients to evaluate the association between the predictive or prognostic variables and the risk of subsequent therapies or survival outcomes.

2. METHODS

2.1. Patients

Between January 2002 and December 2020, we retrospectively collected patients who were aged 12 years or older and who had received radical orchiectomy for testicular cancer followed by systemic chemotherapy. Any patients diagnosed with extratesticular germ cell tumors or sex cord-stromal cell tumors were excluded. The study was approved by the Institutional Review Boards I & II of Taichung Veterans General Hospital, No. CE21365A.

2.2. Study assessment and treatment rationale

All included patients received treatments based on guidance from the multidiscipline oncology team which was composed of urologists, medical oncologists, radiation oncologists, radiologists, and pathologists. The American Joint Commission on Cancer (AJCC) staging system is the standard prognostic clinical staging tool used after a serum markers survey, computed tomography (CT) scan, and radical orchiectomy. However, for treatment purposes, the IGCCCG risk classification is an important guide for either systemic therapy, radiation therapy or surgeries. Patients who initially had normal serum AFP, beta-HCG, and LDH levels, no metastatic lesions in a CT scan or pure seminoma in pathological feature would only undergo the clinical follow-up process and were therefore excluded from this study. By contrast, patients with any elevated tumor markers, radiographically metastatic lesions (regardless of size) or non-seminoma in pathological feature would receive chemotherapy and be included in the study. Bleomycin, etoposide and cisplatin (BEP) were the standard first-line form of chemotherapy. Carboplatin monotherapy was an alternative option in nonmetastatic, elevated serum marker seminoma patients. Patients who had a poor response to first-line chemotherapy or experienced a tumor relapse during the follow-up period would require second-line chemotherapy. Second-line chemotherapy regimens included paclitaxel, ifosfamide, and cisplatin (TIP), cisplatin only, etoposide and ifosfamide (VIP) or ifosfamide only. The regimen decision depended on certain patient factors, such as general performance and adverse events, as well as the disease factors. Third-line treatment was rare, with paclitaxel-based regimens being used.

RPLND or metastasectomy was an important tool beyond first-line chemotherapy both for chemoresponders and nonresponders. The surgeries may be performed once in the operating room or divided into several surgeries due to the different tumor burdens.

In summary, patients who had received any chemotherapy as a form of first-line treatment without any subsequent therapies were placed in the first-line therapy only group. Patients who had received any second-line chemotherapy or metastasectomy were placed in the second-line and beyond group.

2.3. Data assessment

The patient demographic data included continuous variables such as age, serum tumor markers, serum white blood cell count, serum hemoglobin level, serum neutrophil/lymphocyte ratio, and pathologic tumor size. Categorical variables included clinical TNM staging, S stage, regimens of chemotherapy and metastasectomy. Serum tumor markers (alpha fetoprotein [AFP], beta human choriogonadotropin [HCG], and lactate dehydrogenase [LDH]) were determined at the time of staging, before first-line chemotherapy, and at post first-line chemotherapy. Serum biomarkers were collected before first-line chemotherapy. Standard imaging study, including either an abdominal or chest CT scan, or an magnetic resonance imaging (MRI) were performed for staging. The TNM tumor staging was recorded according to the AJCC staging system, testis, 8th edition, including serum marker staging (S stage). Tumor characteristics were recorded as TNM classification, primary tumor size, main histological type of tumor, whether there was lymph nodes metastasis, and S stage. The histological features were recorded as the existence of pure seminoma and the yolk sac feature. The cycles of chemotherapy were recorded separately by the treatment sequence order.

Treatment response was recorded according to both image studies and serum marker results. The standard for the image results was based on The Response Evaluation Criteria in Solid Tumor, version 1.1. Complete response (CR) was defined as the absence of detectable tumor in image studies (CT scan or MRI) after treatment. Partial response (PR) was defined as a 30% decrease in the sum of the diameters of the targeted tumor. Progressive disease (PD) was defined as at least a 20% increase in the sum of the diameters of targeted lesions, while stage disease (SD) was recognized as the diameter change seen in the tumor ranging between PR and PD. Overall survival (OS) was defined as time from the first diagnosis of testicular tumor to death or follow-up date.

2.4. Statistical analysis

Mann-Whitney U and Fisher's exact tests were performed for continuous variables, while the Chi-square test was used for categorical variables. The OS curves were plotted using the Kaplan–Meier method. Cox hazard proportional regression was used to estimate the hazard ratio (HR) among all univariant and multivariant variables, with a 95% confidence interval (CI) for the association between variables and the two study end-points, OS and second-line treatment. p values of <0.05 were regarded as statistically significant. All the statistical analyses were performed using SAS software version 9.2 (SAS Institute, Inc., Cary, NC, USA).

3. RESULTS

There were 150 patients who had received orchiectomy and diagnosed with primary germ cell tumor who were found in our database between January 2002 and December 2020. Sixty-nine patients without adjuvant chemotherapy and 13 who were lost during follow-up were excluded. Ultimately, a total of 68 patients were included in the study. Among them, 40 who did not receive second-line chemotherapy or metastasectomy were referred to the chemotherapy-only group. The remaining 28 patients were categorized as the second-line therapy or more group.

The baseline patient characteristics and demographics are listed in Table 1. The median age was 29.3 years among the first-line therapy–only group compared with 30.6 years in the advanced therapy group (p = 0.784). There were three subjects under the age of 18 in our database who were 15, 16, and 17. Serum tumor markers before orchiectomy were shown to be

Table 1

Baseline characteristics and demographics of testicular cancer patients receiving first-line chemotherapy

	Group		*p*
	Chemotherapy-only group (n = 40)	Second-line therapy group (n = 28)	
Age	29.3 (25.0-35.0)	30.6 (22.3-37.0)	0.784
Serum tumor marker before orchiectomy			
AFP	5.0 (3.0-160.3)	225.0 (8.9-2996.0)	0.004[a]
HCG	26.8 (3.9-488.8)	164.0 (13.6-3018.0)	0.055
LDH	226.5 (183.3-313.8)	661.0 (300.0-1640.8)	<0.001[a]
Serum tumor marker before first chemotherapy			
AFP	4.9 (3.1-51.0)	42.7 (5.0-540.8)	0.058
HCG	1.7 (1.0-288.5)	6.0 (1.4-52.1)	0.545
LDH	209.0 (178.0-266.0)	276.0 (165.3-605.0)	0.290
Serum test before first chemotherapy			
WBC	6850.0 (5500.0-9300.0)	9100.0 (6280.0-10 500.0)	0.064
Hgb	15.4 (14.5-15.7)	13.4 (11.2-14.6)	<0.001[a]
NLR	2.1 (1.7-4.1)	4.1 (2.7-6.8)	0.002[a]
Serum tumor marker after first chemotherapy			
AFP	4.0 (2.5-4.9)	4.8 (2.7-20.6)	0.051
HCG	1.0 (1.0-1.2)	2.0 (1.0-22.3)	<0.001[a]
LDH	178.0 (161.0-191.0)	219.5 (146.3-337.0)	0.081
Metastasis before orchiectomy	11 (28.2%)	24 (85.7%)	<0.001[a]
Primary tumor size, cm	4.5 (3.2-7.0)	8.0 (4.0-10.0)	0.004[a]
Lymph nodes metastasis	21 (53.8%)	22 (78.6%)	0.068
S stage			<0.001[a]
0-1	34 (85.0%)	4 (14.8%)	
2-3	6 (15.0%)	23 (85.2%)	
Histology			
Pure seminoma	16 (40.0%)	6 (21.4%)	-
Have yolk sac cell type	15 (37.5%)	16 (57.1%)	-
Yolk sac (≥20%)			0.047[b]
No	11 (73.3%)	5 (31.3%)	
Yes	4 (26.7%)	11 (68.8%)	
IGCCCG			<0.001[a]
Good prognosis	33 (82.5%)	10 (35.7%)	
Intermediate or poor prognosis	7 (17.5%)	18 (64.3%)	
Receiving RPLND	0 (0.0%)	16 (57.1%)	-
Partial distant organ resection	0 (0.0%)	15 (53.6%)	-
1st line chemotherapy			0.036[b]
BEP	33 (82.5%)	28 (100.0%)	
Carboplatin	7 (17.5%)	0 (0.0%)	
Chemotherapy 1st line cycle	3.0 (1.3-4.0)	4.0 (3.0-5.0)	0.009[a]
Chemotherapy 2nd line			-
BEP	0 (0.0%)	2 (15.4%)	
Ifosfamide	0 (0.0%)	1 (7.7%)	
Ifosfamide + cisplatin + thalidomide	0 (0.0%)	1 (7.7%)	
TIP	0 (0.0%)	3 (23.1%)	
VIP	0 (0.0%)	6 (46.2%)	
Chemotherapy 2nd line cycle	-	3.0 (2.0-4.0)	-
Chemotherapy 3rd line			-
BEP	0 (0.0%)	1 (16.7%)	
Ifosfamide	0 (0.0%)	1 (16.7%)	
Gemcitabine + paclitaxel	0 (0.0%)	2 (33.3%)	
TIP	0 (0.0%)	1 (16.7%)	
VIP	0 (0.0%)	1 (16.7%)	
Chemotherapy 3rd line cycle	-	7.5 (4.3-9.3)	-
Death	1 (2.5%)	6 (21.4%)	0.017[b]
Clinical outcome			<0.001[a]
Complete response	32 (80.0%)	8 (30.8%)	
Progress disease	1 (2.5%)	8 (30.8%)	
Partial response	2 (5.0%)	3 (11.5%)	
Stable disease	5 (12.5%)	7 (26.9%)	
Follow time, mo	34.5 (16.5-69.0)	44.0 (11.5-100.5)	0.690

Chi-square test, Mann-Whitney U test. Median (IQR).

AFP = alpha fetoprotein; BEP = bleomycin, etoposide, and cisplatin; HCG = beta human choriogonadotropin; IGCCCG = International Germ Cell Cancer Collaborative Group; LDH = lactate dehydrogenase; NLR = neutrophil-lymphocyte ratio; RPLND = retroperitoneal lymph node dissection; TIP = paclitaxel, ifosfamide, and cisplatin; VIP = cisplatin, etoposide and ifosfamide; WBC = white blood cell.

[a] $p < 0.01$.

[b] $p < 0.05$.

higher in the second-line therapy group than that seen in the chemotherapy-only group, and were statistically significant in AFP and LDH (AFP: 225 vs 5, $p = 0.004$; HCG: 164 vs 26.8, $p = 0.055$; LDH: 661 vs 226.5, $p < 0.001$). Tumor markers before the first chemotherapy session were higher in the second-line therapy group but not statistically significant (AFP: 42.7 vs 4.9, $p = 0.058$; HCG: 6.0 vs 1.7, $p = 0.545$; LDH: 276 vs 209, $p = 0.290$). Hemoglobin levels before the first chemotherapy session were statistically higher in the chemotherapy-only group (15.4 vs 13.4 g/dL, $p < 0.001$), while neutrophil/lymphocyte ratios were higher in the second-line therapy group (4.1 vs 2.1, $p = 0.002$). White blood cell (WBC) was also higher in the second-line therapy group but did not show any statistical significance (9100 vs 6850, $p = 0.064$). Serum tumor markers after the first chemotherapy session all showed higher in the second-line therapy group but only HCG had any significant difference (AFP: 4.8 vs 4.0, $p = 0.051$; HCG: 2.0 vs 1.0, $p < 0.001$; LDH: 219.5 vs 178.0, $p = 0.081$). Twenty-four (85.7%, 24/28) patients had been diagnosed with metastasis before orchiectomy in the second-line therapy group, while the rate was 28.2% (11/40) in the first-line therapy–only group. The primary tumor size was larger in the second-line therapy group when compared with the chemotherapy-only group (8 vs 4.5 cm, $p = 0.004$). In the chemotherapy-only group, 53.8% of the patients were presented with lymph nodes metastasis compared with 78.6% in the second-line therapy group ($p = 0.068$). There were 15.0% of patients (6/40) recorded as S stage 2–3 in the chemotherapy-only group, whereas the rate was 85.2% (23/28) in the second-line therapy group ($p < 0.001$). The histological data showed that 40% (16/40) of patients were diagnosed with pure seminoma in the chemotherapy-only group, with 21.4% (6/28) being seen in the second-line therapy group. Fifteen patients (37.5%, 15/40) in the chemotherapy-only group had a yolk sac cell component compared with 57.1% (16/28) in the second-line therapy group. Additionally, four (10%, 4/40) patients in the chemotherapy-only group experienced a yolk sac tumor burden larger than 20%, while 11 (39.3%, 11/28) patients in the second-line therapy group experienced the same ($p = 0.047$). Regarding IGCCCG classifications, there were 82.5% (33/40) of patients recorded as a good prognostic risk in the chemotherapy-only group compared with 35.7% (10/28) in the second-line therapy group. In addition, there was one poor risk patient in the chemotherapy group compared with seven in the second-line therapy group. There were 16 (57.1%, 16/28) patients who received RPLND in the second-line therapy group, while 15 (53.6%, 15/28) patients had metastasectomy for distant organs beyond the lymph nodes. In the second-line therapy group, 35.71% (10/28) of the patients made an early switch from chemotherapy to either second-line therapy (6/28) or surgery (4/28) due to a poor response to first-line chemotherapy, with six of them dying from their diseases.

In the chemotherapy-only group, 82.5% of patients (33/40) received a BEP regimen, while 17.5% (7/40) received carboplatin monotherapy, whereas all patients in the second-line therapy group received BEP regimens. The median first-line chemotherapy cycle was higher in the second-line therapy group compared with the chemotherapy-only group (4 vs 3, $p = 0.009$). Thirteen (46.4%, 13/28) patients received second-line chemotherapy in the second-line therapy group. Among them, three received TIP regimens, while the other six received VIP. The median second-line chemotherapy cycle was 3 (range 2.0-3.0). Six patients received third-line chemotherapy, one with BEP, one with ifosfamide only, two with gemcitabine plus paclitaxel, one with TIP, and the final one with VIP. The median third-line chemotherapy cycle was 7.5 (4.3-9.3). One patient (2.5%, 1/40) died in the chemotherapy-only group due to a delayed diagnosis and poor general performance. Six patients died in the second-line therapy group, accounting for 21.4% (6/28) of the patients. Median follow-up duration was 34.5 months in the chemotherapy-only group (range 16.5-69.0 months), and 44.0 months in the second-line therapy group (range 11.5-100.5 months, $p = 0.690$). Fig. 1 reveals the overall survival estimation, with the chemotherapy-only group having a 5-year OS of 92.9% compared with 77.3% in the second-line therapy group ($p = 0.026$).

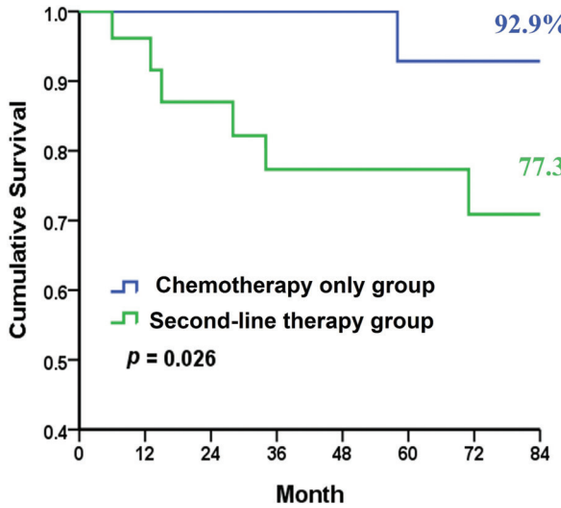

Fig. 1 Overall survival comparison between the chemotherapy-only group and the second-line therapy group. The 5-y overall survival estimation was 92.9% in the chemotherapy-only group and 77.3% in the second-line therapy group.

Table 2 shows univariate analysis for overall survival after orchiectomy. A higher S stage and the receiving of second-line therapies showed a trend of increased death risk (HR = 8.26, 95% CI, 0.99-68.67, $p = 0.051$; HR = 7.76, 95% CI, 0.93-64.99, $p = 0.059$, respectively).

Analysis of the association between the variables and the risk of receiving second-line therapy demonstrated that S stage 2 or 3 was an independent factor with regards to receiving subsequent therapy (HR = 41.38; 95% CI, 3.71-461.71, $p = 0.002$, Table 3).

4. DISCUSSION

The endpoints of this study are to identify the prognostic and predictive factors associated with overall survival or subsequent therapies among Taiwanese advanced testicular cancer patients who will receive first-line chemotherapy. Ultimately, we found that baseline S stage 2 to 3 was associated with a higher risk of either subsequent second-line chemotherapy or surgery (HR = 41.38, $p = 0.002$). This indicator can assist in the pretreatment planning of patients in terms of ordinary life, studies, work, and even marriage and childbirth among the young men who have been diagnosed.

Medical prognostic factors, including basic patient characteristics, serum marker levels, pathologic features, and clinical stages were widely reported. However, nonseminoma seen in pathology, high serum tumor markers, large tumor size, vascular invasion, epididymis invasion, high risk in IGCCCG classifications, and a high clinical stage may all have a correlation to clinical definition, resulting in statistical confounding during multivariate analysis. Therefore, the reported prognostic factors usually vary from one study to another due to different designs and databases.[3,6–9] Xu et al[10] identified that age over 20 at diagnosis, NSGCT histology (HR = 1.69), tumor size larger than 5 cm (HR = 1.92), AJCC stage III (HR = 3.85), and number

Table 2

Univariate analysis for overall survival after orchiectomy

	Hazard ratio (95% CI)	*p*
Age	1.02 (0.93-1.11)	0.741
Tumor size, cm	1.08 (0.84-1.38)	0.542
S stage		
0-1	Reference	
2-3	8.26 (0.99-68.76)	0.051
IGCCCG		
Good prognosis	Reference	
Intermediate or poor prognosis	2.22 (0.49-9.95)	0.299
Cell type		
SGCT	Reference	
NSGCT	0.99 (0.19-5.21)	0.995
Serum tumor marker		
Before first chemotherapy		
AFP	1.00 (1.00-1.00)	0.835
HCG	1.00 (1.00-1.00)	0.143
LDH	1.00 (1.00-1.00)	0.897
After first chemotherapy		
AFP	0.97 (0.83-1.14)	0.707
HCG	1.00 (1.00-1.00)	0.136
LDH	1.00 (1.00-1.00)	0.293
Serum test		
WBC	1.00 (1.00-1.00)	0.491
Hgb	0.86 (0.62-1.19)	0.361
NLR	1.00 (0.92-1.07)	0.909
Chemotherapy 1st line		
BEP	Reference	
Carboplatin	-	
Chemotherapy 1st line cycle	1.67 (0.90-3.13)	0.106
Group		
Chemotherapy only	Reference	
Second-line therapy or more	7.76 (0.93-64.99)	0.059
Clinical outcome		
CR	Reference	
Non-CR	-	

Cox proportional hazard regression.

AFP = alpha fetoprotein; BEP = bleomycin, etoposide, and cisplatin; CR = complete response; HCG = beta human choriogonadotropin; IGCCCG = International Germ Cell Cancer Collaborative Group; LDH = lactate dehydrogenase; NLR = neutrophil-lymphocyte ratio; NSGCT = nonseminomatous germ cell tumor; SGCT = seminomatous germ cell tumor; WBC = white blood cell.

of metastatic sites were all independent risk factors for overall survival among testicular cancer patients taken from the Surveillance, Epidemiology and End Results (SEER) database. These pathologic factors were similar to previous studies which showed the importance of embryonal cell carcinoma percentage as a prognostic factor. However, while implementing IGCCCG classification and AJCC staging, the impact of pathologic subtypes became nonsignificant.[11–14] Similar results were observed in the neutrophil/lymphocyte ratio studies performed by Fossa et al and Tan et al.[15–18] Despite the controversy surrounding serum markers and pathologic subtypes, the importance of AJCC staging is consistent among each study.[9,18] In our study, because the AJCC staging system may have overlapped the IGCCCG classifications, we divided the AJCC features into several variables while working on risk analysis. All variables were not significantly associated with overall survival statistically. Only S 2-3 and the receiving of second-line therapies showed a trend of increased death risk. This could be the influence of having analyzed just a small population, since only 11.76% (8/68) of IGCCCG poor risk patients were included.

Chemotherapy regimens varied within our study population. Two of the second-line BEP patients relapsed 2 and 3 years after first-line chemotherapy. Both patients then received RPLND and survived. The third-line BEP patient was resistant to two prior chemotherapy sessions and eventually succumbed to the disease. Seven patients in the chemotherapy-only group received carboplatin monotherapy, with all seven given a good IGCCCG prognosis, an S1 stage evaluation and receiving adjuvant carboplatin monotherapy at a dosage of 7 AUC as previously reported. Several studies have shown that one or two doses of carboplatin was associated with reduced relapse and low toxicity. In our experience, the clinical results of these seven patients also showed no recurrence after a single dose of carboplatin.

Regarding the use of carboplatin in the treatment of advanced testicular cancer, it was shown to be inferior to cisplatin combination therapy. In our series, carboplatin was not used in the metastatic or intermediate stages in poor prognosis patients.

Woldu et al[5] retrospectively analyzed 5062 men diagnosed with stage II/III NSGCT from the National Cancer Data Base in the United States. Age, comorbidity, nonprivate insurance, distance from hospital, clinical stage, and risk group were all found to be independently associated with all-cause mortality. This is the first published large cohort to identify nonbiological issues associated with advanced testicular cancer outcomes. The rationale for the results may be related to a delay in diagnosis and continuous treatment for a low socioeconomic status population.[19] Their findings corresponded to another Hungarian group in which a parent's education level was associated with patient delay.[20] However, while the lower social quartile was associated with higher mortality, it was not related to more advanced stages. There was no direct evidence regarding one's socioeconomic association being a factor in our series. Among the seven cancer-specific death patients, only one had a parenting problem and was aged under 18. In Taiwan, the national health insurance program covers 99.5% of the total population, so cancer-related medical fees are completely reimbursed. The influence of racial or insurance status in our study was not comparable to those in the SEER database.[19,21]

Although many prognostic variables detected a poor overall survival, any prediction surrounding treatment outcome after first-line chemotherapy remains difficult. Pathologists have revealed some protein expression in testicular cancer tissue, such as octamer-binding transcription factor 4, may associated with lymphovascular invasion and embryonal carcinoma.[22] Recent advances using RNA-binding proteins have been used to create a risk score for predicting progression-free survival and overall survival among germ cell tumor patients from The Cancer Genome Atlas database.[23] These tools, combined with IGCCCG risk classifications, are being used as current clinical guidance for systemic chemotherapy and RPLND. Our findings reveal a clear indicator for patients who have received first-line chemotherapy that the risk of taking subsequent second-line chemotherapy or surgeries was 33.13 times while the serum marker was at stage 2 to 3.

Limitations to the study include the retrospective study design, small patient population, unadjusted patient management, and lack of detail surrounding family education levels and socioeconomic data. Additionally, rather than using AJCC staging, we selected IGCCCG combined with other histological features while working on risk factors analysis. Therefore, analysis results may differ from other series. Furthermore, RPLND is not regarded as an important first-line tool in the management of advanced testicular tumors. This management process change can influence results, particularly in a small population study.[24]

In conclusion, patients at serum tumor marker stage 2 to 3 showed an increased risk of receiving subsequent second-line therapies, including chemotherapy or surgeries. For these young

Table 3

Univariate and multivariate analysis for patients receiving second-line therapy or more

	Univariate		Multivariable		
	Odds ratio (95% CI)	***p***	**Odds ratio**	**(95% CI)**	***p***
Age	0.99 (0.94-1.05)	0.769			
Tumor size, cm	1.29 (1.07-1.55)	0.008[a]			
S stage					
0-1	Reference		Reference		
2-3	32.58 (8.27-128.40)	<0.001[a]	41.38	(3.71-461.71)	0.002[a]
IGCCCG					
Good prognosis	Reference		0.49	(0.04-5.37)	0.557
Intermediate or poor prognosis	8.49 (2.76-26.10)	<0.001[a]			
Cell type					
SGCT	Reference				
NSGCT	2.44 (0.81-7.36)	0.112			
Serum tumor marker					
Before first chemotherapy					
AFP	1.00 (1.00-1.00)	0.562			
HCG	1.00 (1.00-1.00)	0.891			
LDH	1.00 (1.00-1.00)	0.142			
After first chemotherapy					
AFP	1.20 (0.93-1.53)	0.156			
HCG	1.00 (1.00-1.00)	0.357			
LDH	1.01 (1.00-1.02)	0.029[b]			
Serum test					
WBC	1.00 (1.00-1.00)	0.051			
Hgb	0.59 (0.42-0.82)	0.001[a]	0.79	(0.54-1.17)	0.236
NLR	1.00 (0.95-1.04)	0.936			
Chemotherapy 1st line					
BEP	Reference				
Carboplatin	-				
Chemotherapy 1st line cycle	1.58 (1.10-2.28)	0.014[b]			
Clinical outcome					
CR	Reference				
Non-CR	9.00 (2.89-28.07)	<0.001[a]			

Logistic regression.

AFP = alpha fetoprotein; BEP = bleomycin, etoposide, and cisplatin; CR = complete response; HCG = beta human choriogonadotropin; IGCCCG = International Germ Cell Cancer Collaborative Group; LDH = lactate dehydrogenase; NLR = neutrophil-lymphocyte ratio; NSGCT = nonseminomatous germ cell tumor; SGCT = seminomatous germ cell tumor; WBC = white blood cell.

[a]$p < 0.01$.

[b]$p < 0.05$.

men, both thorough therapeutic planning and life style modification can be helpful during their treatment journey.

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