Original Article

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Treatment and Management in Relapsed/Refractory Malignant Somatic Transformation

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Abstract

Objective: To demonstrate treatment responses, survival analysis and treatment-related mortality characteristics of patients with malignant somatic transformation (MST).

Materials and Methods: In this retrospective cross-sectional study, patients with relapsed and refractory MST who had previously received multiple-line chemotherapy were evaluated. Clinical features and follow-up data of relapsed/refractory MST patients were recorded from the patients' registration database at the hospital. Age, clinical stage at initial diagnosis, serum tumour marker levels, visceral metastasis status, previous treatment protocols and follow-up times were recorded. This study aims to demonstrate demographic and disease-related characteristics, best response to systemic therapy, and overall survival (OS) results.

Results: The study included 14 patients. Mean age at diagnosis was 29.6 years for the whole group. The most-common sarcoma subtype was Ewing sarcoma (44.4% in the sarcoma group). In half the patients, the best response to systemic treatment was determined as a complete response. Median OS for the sarcoma group was 19.72 months [interquartile range (IQR) 29.18 months], and in the adenocarcinoma group, it was determined as 136.24 months (IQR 131.92 months) (p=0.006). The median OS for the whole group was 28.12 months (IQR 99 months). No significant difference in survival was found between synchronous and relapsed cases [median (IQR) 24.09 (91.23) months vs 43.54 (113.51) months, p=0.606].

Conclusions: Germ cell tumour patients with MST should be treated according to the somatic component. Poor responses to cisplatin-based chemotherapy have been found in this cohort. Patients with sarcomatous components were found to have significantly shorter OS.

Keywords: Germ cell tumour, malignant somatic transformation, teratoma, testicular cancer

Introduction

Germ cell tumours (GCTs) are one of the most-common solid malignancies in the male population, especially in the second and third decades of life (1). Even if patients are diagnosed at an advanced stage, a very good response can be obtained, especially with the platinum-based treatment approach. The five-year overall survival (OS) for advanced disease is 80-90% (2).

By contrast, it is known that, rarely, testicular teratomas can undergo malignant somatic transformation (MST) (3). MST is a phenomenon seen in 2.7-8.6% of non-seminomatous GCTs. The most-common transformed histologic types include rhabdomyosarcoma, adenocarcinoma, and primitive neuroectodermal tumour (4,5). MST is a difficult clinical entity to treat because of its chemoresistance to platinum-based therapies and frequent recurrence. Despite all oncological treatment options, survival rates are low even in reference health centers (6).

Since studies on this subject are limited to case reports, it is difficult to understand the prognostic factors of cases with MST and to manage the treatment process. No significant difference in survival has been reported between secondary histopathological subgroups in most studies (5,7). To the best of our knowledge, in relation to our country, anecdotal case series of MST patients have been reported.

We retrospectively evaluated the clinical features of all cases with MST treated at University of Health Sciences Turkey, Gülhane Training and Research Hospital in Ankara, Turkey. We focused on the presentation differences between the histological subtypes of MST, the time frame in which MST occurs, and the therapeutic approach used to understand the response to treatment. We aimed to show the prognostic factor differences and survival difference between sarcomatous transformation and carcinomatous transformation.

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Materials and Methods

We conducted this study by retrospectively reviewing the medical records of outpatients and inpatients with MST from a tertiary clinic from January 2017 through June 2021. The inclusion criteria were age ≥18 years, a histologically confirmed metastatic testicular cancer, imaging-proven metastases and confirmed somatic transformation at diagnosis or at recurrence. The exclusion criteria were age <18 years and insufficient clinical data.

We identified a total of 14 patients. Age at diagnosis, synchronous vs metachronous detection of MST, localization of primary lesion, localization of MST, histopathological subtypes of MST, serum tumour marker status at first diagnosis, International Germ Cell Cancer Collaborative Group (IGCCCG) risk classification at initial diagnosis, visceral metastasis status, treatments for MST (surgery, radiotherapy and systemic treatments), survival after MST diagnosis and OS time from first diagnosis were retrieved from medical records (8). Time from initial diagnosis to the patient's last hospital admission or death was defined as OS. The University of Health Sciences Turkey, Gülhane Training and Research Hospital Clinical Research Ethics Committee approved the study protocol (decision number: 2021/57).

Complete remission was defined as the disappearance of all clinically and radiologically detectable lesions and the normalization of tumour markers. More than 20% reduction in tumour burden was defined as a partial response. Tumour growth greater than 20% was defined as progressive disease. Any other response was classified as stable disease.

Statistical Analysis

Descriptive statistics are presented as a percentage of the total. Uniformity of continuous variables to normal distribution was examined using the Kolmogorov-Smirnov test. Normally distributed continuous data are expressed as mean ± standard deviation, and data not normally distributed are expressed as median [interquartile range (IQR)]. Differences between groups according to distribution and type of variable were tested with Pearson's chi-squared test, Student's t-test or Mann-Whitney U test. A p-value less than 0.05 was considered statistically significant. We performed statistical analyses using SPSS 22.0 software (SPSS Inc., Chicago, Illinois).

Results

The mean age of the group at initial diagnosis was 29.6 years, and the most-common localization of the primary tumour was the testicles (78.6%). Patients were often identified as stage 3C at the time of initial diagnosis (71.4%). Most patients had a sarcomatous histological subtype (64.2%), and also in most patients, MST was detected at the time of relapse (57.1%). The most-common sarcoma subtype was Ewing sarcoma (44.4%). Colon cancer was the most-common adenocarcinoma subtype (40%). At the diagnosis, serum tumour marker level at S3 was detected in 42.9% of the patients. In the IGCCCG risk classification evaluation, the majority of patients were included in the "poor" risk group (78.6%). Orchiectomy was performed in all patients with primary testicular cancer (Table 1). Surgery to the MST lesion was performed in most patients (64.3%). Half the patients with MST lesions received radiotherapy with or without surgery. All patients received systemic chemotherapy. In half the patients, a complete response was obtained as the best response. Median OS for the sarcoma group was 19.72 months (IQR 29.18 months). In the adenocarcinoma group, it was determined as 136.24 months (IQR 131.92 months) (p=0.006). Mean OS for the whole group was 28.12 months (IQR 99 months) (Table 2 and Figure 1). No significant difference in survival was observed between synchronous and relapsed cases [median (IQR) 24.09 (91.23) months vs 43.54 (113.51) months, p=0.606].

Table 1. The demographic and disease-related characteristics of the patients

Features	Sarcoma (n=9)	Adenocarcinoma (n=5)	Total (n=14)
Age, median (range), years	23 (18-40)	42 (20-49)	26.5 (18-49)
Location of primary, n (%)			
Testes	7 (77.7)	4 (80)	11 (78.6)
Retroperitoneal	1 (11.1)	1 (20)	2 (14.3)
Mediastinal	1 (11.1)	0 (0)	1 (7.1)
Time of diagnosis of MST, n (%)			
Synchronus	5 (55.5)	1 (20)	6 (42.9)
Relapse	4 (44.4)	4 (80)	8 (57.1)
Clinical stage (AJCC, 8th), n (%)			
II B	2 (22.2)	0 (0)	2 (14.3)
II C	2 (22.2)	0 (0)	2 (14.3)
III C	5 (22.2)	5 (100)	10 (71.4)
Serum tumor markers, n (%)			
S0	5 (55.5)	1 (20)	6 (42.9)
S1	1 (11.1)	1 (20)	2 (14.3)
S2	0 (0)	0 (0)	-
S3	3 (33.3)	3 (60)	6 (42.9)
IGCCCG risk groups, n (%)			
Good risk	1 (11.1)	0 (0)	1 (7.1)
Intermediate risk	2 (22.2)	0 (0)	2 (14.3)
Poor risk	6 (66.6)	5 (100)	11 (78.6)
Visceral metastasis, n (%)			
Lung	5 (55.5)	4 (80)	9 (64.3)
Liver	4 (44.4)	3 (60)	7 (50)
Bone	2 (22.2)	1 (20)	3 (21.4)
Orchiectomy	7 (77.7)	4 (80)	11 (78.6)

MST: Malignant somatic transformation, AJCC: The American Joint Committee on Cancer, S1: Lactate dehydrogenase (LDH) <1.5 × Upper limit of normal (ULN) and human chorionic gonadotropin (hCG) (mIU/mL) <5000 and alpha-fetoprotein (AFP) (ng/mL) <1000. S2: LDH 1.5 to 10 × ULN or hCG (mIU/mL) 5000 to 50,000 or AFP (ng/mL) 1000 to 10,000. S3: LDH >10 × ULN or hCG (mIU/mL) >50,000 or AFP (ng/mL) >10,000. IGCCCG: The International Germ Cell Cancer Collaborative Group

Discussion

The development of MST in GCT patients is a very rare condition. Because of this, there is a lack of data on MST and, therefore, a lack of a general approach. Widespread differences in inclusion criteria in the reported case series preclude generalization of study findings for this already-small number of patients.

MST, which develops from different germinal layers as its histological origin, is considered to be a clinical entity that exacerbates the prognosis. It is a phenomenon with a tendency to transform into systemic disease and invade local tissues. MST is often resistant to the chemotherapy used to treat GCTs. Therefore, in a significant proportion of patients, surgical resection remains the only potentially curative approach (9,10).

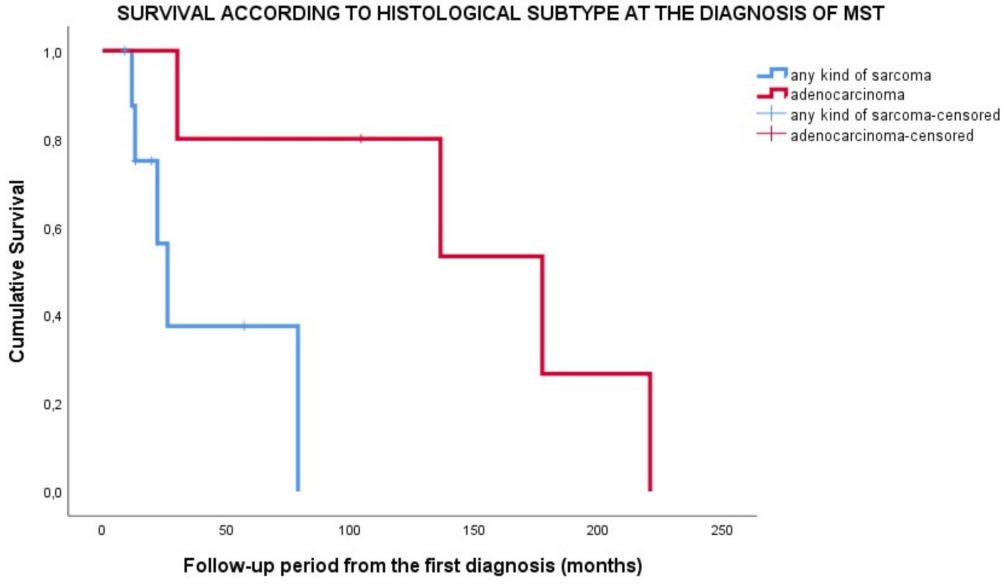

Figure 1. Survival according to histological subtype at the diagnosis of MST

MST: Malignant somatic transformation

Table 2. Treatment-related characteristics of the patients

Features	Sarcoma (n=9), n	Adenocarcinoma (n=5), n	Total (n=14), n (%)
Surgery to MST, n (%)	7 (77.7)	2 (40)	9 (64.3)
Radiotherapy to MST, n (%)	5 (55.5)	2 (40)	7 (50)
Systemic treatment of MST, n (%)	9 (100)	5 (100)	14 (100)
First line systemic treatment for MST, n (%)			
ICE	2 (22.2)	1 (20)	3 (21.4)
VAC-IE	4 (44.4)	0 (0)	4 (28.6)
FLOT	0 (0)	1 (20)	1 (7.1)
FOLFOXIRI-bevacizumab	0 (0)	1 (20)	1 (7.1)
Cisplatin + gemcitabine	0 (0)	1 (20)	1 (7.1)
IMA	2 (22.2)	0 (0)	2 (14.3)
VAC	1 (11.1)	0 (0)	1 (7.1)
FOLFOX	0 (0)	1 (20)	1 (7.1)
Best response to systemic treatment for MST, n (%)			
Complete response	6 (66.6)	1 (20)	7 (50)
Partial response	0 (0)	2 (40)	2 (14.3)
Stable disease	1 (11.1)	2 (40)	3 (21.4)
Median overall survival, median (IQR), months	**19.72 (29.18)**	**136.24 (131.92)**	**28.12 (99)**

MST: Malignant somatic transformation, ICE: Ifosfamide, carboplatin, etoposide, VAC-IE: Vincristine, adriamycin, cyclophosphamide, ifosfamide, etoposide, FLOT: Fluorouracil, oxaliplatin, docetaxel, FOLFOXIRI: Fluorouracil, oxaliplatin, irinotecan, IMA: Ifosfamide mesna adriamycin, VAC: Vincristine, adriamycin, cyclophosphamide, FOLFOX: Fluorourasil, oxaliplatin, IQR: Interquartile range

As in the previously reported case series, sarcomatous transformation was mostly detected in our patients. While rhabdomyosarcoma is the dominant component in case series, the most-common sarcomatous component in our series is Ewing sarcoma (11). Primary tumour location was predominantly in the testes. Scheckel et al. (6) also reported the most-common primary site as the testicles in a case series of 24 patients. The effect of the detection of synchronous or relapsed MST on survival has been the subject of ongoing speculation. Rice et al. (11) reported one of the largest series on this subject and stated that MST detected at relapse had a shorter cancer-specific survival. In our cases, although the survival difference was numerically shown in the synchronous and relapsed patient groups, no significant results were identified.

It has been reported in previous series that clinical staging and IGCCCG classification, which are the leading schemes showing the prognosis used in GCT, are not effective for use in the case of MST (11,12). Instead, the histological grade of the sarcomatous transformation and MST detection in relapse have been associated with prognosis (3,13). However, Colecchia et al. (14) found the stage at initial diagnosis to be a strong prognostic factor associated with the disease in their series of 40 patients. The patients in our study were detected in the advanced clinical stage according to the American Joint Committee on Cancer. This may be the reason we could not detect a survival difference between the groups.

For MST, the presence of visceral metastases is considered a poor prognostic factor for a condition that is already considered chemoresistant. In a series of 33 cases reported by Guo et al. (7), the presence of metastases in MST was shown to be associated with a higher mortality rate.

Surgical resection is considered the main element of treatment, and access to centers that can provide advanced surgical care is important. There are also reports suggesting that, if the MST is limited to the primary testicular GCT, there may be no difference in survival between GCTs with MST and GCTs (15). It can be considered advantageous to provide direct local treatment by performing orchiectomy, especially in the detected testicular mass.

Administration of chemotherapy after resection is widely accepted, but in contrast to highly curable testicular GCTs, chemoresistance to standard cisplatin-based regimens is common in MST (16). Therefore, the main factor that guides systemic treatment in MST is the histologically dominant component. In our cases, adriamycin-containing regimens were generally used with patients with sarcomatous transformation, whereas fluorouracil-containing regimens were preferred in cases with adenocarcinoma since they were generally of gastrointestinal origin (16,17).

There are discrepancies in the data on survival of patients with MST. Some reports have stated that histological subtype has no effect on survival. Others have reported that the carcinoma subtype results in better survival than sarcomatous transformation (5,18). In our cases, we found that the adenocarcinoma group had a significantly longer survival than the sarcomatous group.

Study Limitations

This paper has several limitations. First, the number of cases is limited. Although the time interval in which the series reported in the literature were collected is much wider than our time interval, we present one of the largest case series from our country as a single center, to the best of our knowledge. MST is an extremely rare clinical entity. Even in clinics that follow a high percentage of GCT patients, few cases are seen. We believe that we will be able to present new evaluations in the future with the follow-up and increase of our cases in this regard. Second, because our study is a retrospective analysis, the assurance of the accuracy of the records is limited. Such studies may involve bias in record-keeping ability. Third, the present study has a cross-sectional design. Therefore, the results cannot be assumed to be causal. Additionally, our study includes GCTs of mixed tissue origin, such as the mediastinum, retroperitoneum, and testes, which are known to have different clinical outcomes. Finally, although a significant difference in OS was detected between the groups, the small sample size limits definitive results.

Conclusion

Our cases primarily highlight the difficulty in the follow-up and treatment of patients with MST and GCT, as well as the need for a multidisciplinary treatment approach as the basis for successful management. The study aimed to contribute to the literature in this field, which consists of anecdotal case series, in general, from the Turkish patient population.

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Ethics

Ethics Committee Approval: The University of Health Sciences Turkey, Gülhane Research and Training Hospital Clinical Research Ethics Committee approved the study protocol (decision number: 2021/57).

Informed Consent: Retrospective cross-sectional study.

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Authorship Contributions

Concept: M.B.A., N.K., Design: M.B.A., R.A., Supervision: B.Y., İ.E., N.K., Data Collection-Processing: G.S.Y., N.İ., Analysis-Interpretation: M.B.A., Literature Review: G.S.Y., N.İ., R.A., Writing: M.B.A., Critical Review: B.Y., İ.E., N.K.

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