ORIGINAL RESEARCH PAPER

Volume-7 | Issue-2 | February-2018 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

LONG TERM SURVIVAL OF PRIMARY MEDIASTINAL GERM CELL TUMOURS: EXPERIENCE FROM A TERTIARY CANCER CENTER IN KERALA

Oncology

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ABSTRACT

Malignant germ cell tumour (GCT) in the mediastinum is a rare entity in routine clinical practice. Aim of the study was to assess long-term survival of primary mediastinal GCTs and the factors influencing the outcome of patients treated at Regional Cancer Centre (RCC), Trivandrum.

Materials and methods : Patients registered at RCC, Trivandrum, during 2005-2010, were included (n=15). We retrieved the medical records of patients diagnosed with mediastinal GCT and were followed-up until September 2017. The median follow-up is 89.2 months.

Results: The mean age was 25 years (SD: 7.8 years). All were males. Marker response to treatment was observed in 11/12 patients who had elevated markers initially. After the planned course of chemotherapy, 8 patients were disease-free (clinically and radiologically) and the rest 6 patients had residual disease. Of the 6 patients, 4 underwent surgery and 2 had viable tumour after surgery. During the follow-up, one patient who was disease free, died of acute cardiac event, 3 relapsed. The 8-year overall survival was 66% (SE: 12.4%) and 8-year disease-free survival was 77% (SE: 12%).

Conclusion: Our institutional experience showed that platinum based chemotherapy regimens, surgery and efficient supportive management, the survival of GCTs could be improved in this modern era

KEYWORDS

primary mediastinal germ cell tumour, adult GCT, mediastinal tumours

Introduction

Primary mediastinal germ cell tumour is a rare entity in routine clinical practice. It constitutes approximately 15% of all mediastinal tumours in adults (Travis et al., 2004). They occur in all age group ranging from childhood to elderly population. Mediastinum is considered as the most common site of extragonadal germ cell tumour (Raghavan et al., 1991). Primary mediastinal GCTs have different clinical characteristics when compared with their testicular counterparts , even though they share similar histologic and serologic features. Because of the differences in their clinical behaviour and genetic characters they have been commonly classified as prepubertal and postpubertal tumors (Shnieder et al., 2002). Prepubertal mediastinal GCTs account for approximately <5% of all germ cell neoplasms (Shnieder et al., 2004). Tumors arising in this area constitute a heterogeneous group of diseases, majority of them carry a dismal prognosis, but few of these tumours, especially GCT, are curable and have a good prognosis. Yolk sac tumor predominates mainly in girls with a female-to-male ratio of 4:1. (Takeda et al., 2003). Teratomas do not possess any sex predilection. Postpubertal mediastinal GCT mainly occur in men (Dulmet et al., 1993). The most common histologic type in this group is teratoma, seminoma is the second common type in this age group (Dulmet et al., 1993, Moran and Suster 1998). They occur mainly in men but very rare cases have been reported in females also. Same is the case with yolk sac tumor in post pubertal population (Moran and Suster, 1997).

Even though many theories have been proposed, the histologic origin of mediastinal GCT still remains controversial. One theory suggests that mediastinal GCT may be due to a reverse migration from an occult GCT of the gonads. This theory is based on studies which compared the genetic alterations of both the gonadal and extra gonadal germ cell tumours. The occurrences of recurring breakpoints were not different significantly between them (Chaganti et al., 1994). Another theory says that during some point in the embryogenesis, local transformation of primordial germ cells that migrated from the yolk sac to the genital ridge become misplaced in the midline (Witschi et al., 1948).

Patients with Klinefelters syndrome have a strong association with mediastinal GCT; studies have reported that the risk is about 50 to 100-fold. It has been noted that the peak age is 10 years earlier in this population (Schmoll et al., 2002).

Common symptoms of this disease are dyspnoea, chest pain, cough, superior venacaval obstruction, hoarseness of voice, hemoptysis, dysphagia, fever and weight loss in the order of their decreasing frequency. Rarely, symptoms due to hormonal problems like gynecomastia, testicular atrophy and precautious puberty can occur as presenting features. Elevated serum tumour markers [alfa-feto protein (AFP), beta human chorionic gonadotropin] also help in diagnosing and differentiating these tumours, similar to their gonadal counterparts.

The differential diagnosis of mediastinal GCT includes, thymomas, thymic carcinomas, lymphomas, metastatic lymph node, thymic cysts, thyroid masses, neurogenic tumors and soft tissue tumors.

With this background information, the present analysis aims to assess the clinical profile, treatment & factors influencing the outcome and long-term survival of primary mediastinal GCTs treated at Regional Cancer Centre (RCC), Trivandrum, during a time period of five years.

Materials and Methods

Patients registered at RCC, Trivandrum, during the period 2005 to 2010, were included in the study. After obtaining approval from our

institutional review board, we retrieved and analysed the medical records of patients diagnosed with mediastinal germ cell tumours. We assessed the clinical profile and treatment outcomes of these patients. A total 15 cases of primary mediastinal GCT's treated at RCC Trivandrum from 2005 to 2010 are included in the study. The patients were followed up until September 2017. Descriptive statistics such as frequency distribution, mean and standard deviation were obtained. We used Kaplan-Meier method for overall and disease-free survival estimation.

Results

The mean age was 25 years (range 15-42 years, SD: 7.8 year). All were males. Common presenting symptoms were dyspnoea (n=9), chest pain (n=3), cough (n=2) and superior venacaval obstruction (n=1). The patients were evaluated with clinical examination, CT scan of chest, abdomen, ultrasonography of testes and serological tests.

Only 2 (13.3%) patients had metastases at presentation, both were pulmonary. Serum AFP was elevated in 4 patients, normal in 10 patients and not available in one patient. Serum beta hcg was elevated in 12 patients, normal in 2 patients and not available in 1. Serum LDH was elevated in 8 patients, normal in 1 patient and not available in 6 patients. Biopsy of the tumour was performed in all patients except 1 (who presented with features of SVCO and treatment was started on the basis of clinical, radiological and serological diagnosis of germ cell tumour). Amongst the rest 14 patients, 12 were non-seminoma and 2 were seminoma. All patients received chemotherapy. All patients had regular follow-up once every 2 months for two years and at increasing intervals thereafter. Patients were followed up clinically, radiologically and serologically.

Majority of the patients received chemotherapy with BEP regimen-Bleomycin, Etoposide and Platinum- (9 out of 15). Four patients received EP regimen (etoposide and platinum), one patient received VIP (vinblastin, ifosamide and platinum) regimen. One patient presented with very poor general condition and was given single agent carboplatin (Table 1).

Three patients had treatment interruptions (1 had bleomycin toxicity, 1 had grade 4. neutropenia, 1 patient was hospitalized due to acute psychiatric event. All patients except one, who presented with poor general condition had completed the full course of planned chemotherapy. This patient died of acute cardiac event after the first cycle of chemotherapy. Marker response to treatment was observed in 11 out of 12 patients who had elevated markers initially.

After the planned course of chemotherapy, 8 patients were disease free clinically and radiologically and the rest 6 patients had residual disease. Out of these 6 patients, 4 were operable. They underwent surgery and only 2 had viable tumour after surgery. Median follow-up was 89 months (range: 3-144 months).

After completion of the planned course of cisplatin based combination chemotherapy 91% of our patients had marker response. Among the 14 who took treatment, 57% had complete response, 42% had residual disease, out of them 66% could undergo secondary resection. Half of them had viable tumour and they were offered two more courses of chemotherapy.

The median follow-up was 89.2 months. During the follow-up period, one patient who was disease free, died of acute cardiac event. Three patients relapsed. One patient presented with loss of appetite and found to have marker relapse and extensive liver metastasis and was initiated on 2nd line chemotherapy with VIP regimen. But patient's general condition deteriorated after the first cycle so further treatment was not given and later succumbed to disease. One patient presented at nearby Government medical college hospital with local and systemic relapse. He expired after three months while on treatment there. The third patient reported to our emergency department with severe breathlessness. Radiological examination revealed local and systemic relapse. He died on the same day. At the time of follow-up period, ten patients were alive and disease free (Flow chart 1). The 8-year overall survival was 66% (SE: 12.4%) and 8-year disease free survival was 77% (SE: 12%) (Figures 1 & 2).

Discussion

In the present study, all patients with mediastinal GCTs were males. Another study from the same institute by Jyothirmayi et al.,, reported in 1997, all patients were males (Jyothirmayi et al., 1997). Similar pattern of only males were reported in some studies (Moran and Suster, 1997). Even though male preponderance was observed, some studies reported female mediastinal GCTs also. A single Japanese institution, who published 50 years of experience, which is one of the largest series, out of 129 patients, only 54% were males (Takeda et al., 2003). In the present study, the mean age was 25 years (range: 15-42 years). Other studies also reported almost same mean age (Jyothirmayi et al., 1997; Takeda et al., 2003).

The most common presenting symptoms reported in our study was dyspnoea followed by chest pain and cough. In contrast to this, in the study by Takeda et al.,(2003), it was chest pain followed by dyspnoea and cough (Takeda et al., 2003).

Majority of our GCTs were non-seminomatous, the proportion of seminoma was considerably low. 12 were non seminoma and only 2 were seminoma out of the 14 cases. One patient, who did not have biopsy proof, had elevated tumour markers. The 50 years' experience published Osaka University Graduate School of Medicine, Japan, reported 56 cases of malignant GCT, of which 24 were seminomas and 32 were NSGCT (Takeda et al., 2003). In the 30-year experience of Paris-Sud University by Dulmet et al (1993), out of 40, 16 were seminoma and the 24 were NSGCTs. But in these two studies teratoma was a significant histological entity (Dulmet et al., 1993).

At the time of reporting, 10 patients were alive and disease free. The 5 year OS in the series reported from our centre earlier (Jyothirmayi et al., 1997) was 44%. In the series reported by Bokemeyer et al. (2002) 5-year OS was 45% . Our study was conducted in the period 2005 to 2010 which is relatively recent compared to the other published series. Our 8-year OS is 66% and 8 year DFS is 77%. Compared to the previous era, better chemotherapy regimens, aggressive surgery and efficient supportive care including the management of treatment related complications all might have added to the better survival in this era.

There are only limited publications about mediastinal germ cell tumours in recent years. Most of the studies have only limited number of patients which does not allow to define treatment strategies. Majority of studies have published their 30 to 50 years results.

In conclusion, our institutional experience showed that with platinum based combination chemotherapy regimens, surgery and efficient supportive management, the survival of GCTs could be improved in this modern era.

Table 1. Chemotherapy used for primary mediastinal germ-cell tumours

Chemo regimen	Number of cycles	Number of patients (%)
BEP	4	8 (53.3)
BEP	3	1 (6.7)
EP	4	4 (26.6)
VIP	6	1 (6.7)
Carboplatin	1	1 (6.7)

Flow chart 1: Primary mediastinal germ-cell tumours treated at Regional Cancer Centre, Trivandrum during 2005-10

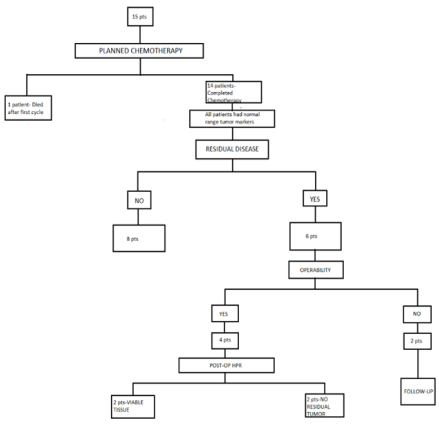


Figure 1. Overall survival of mediastinal germ-cell tumour

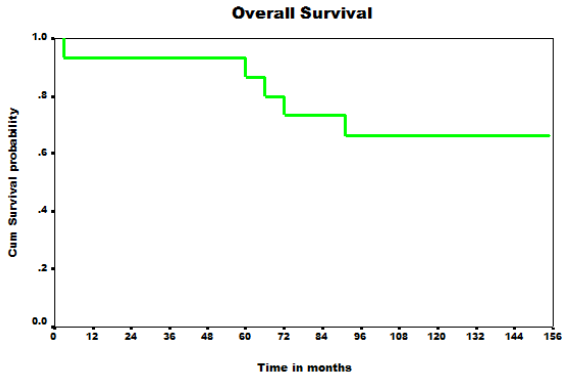
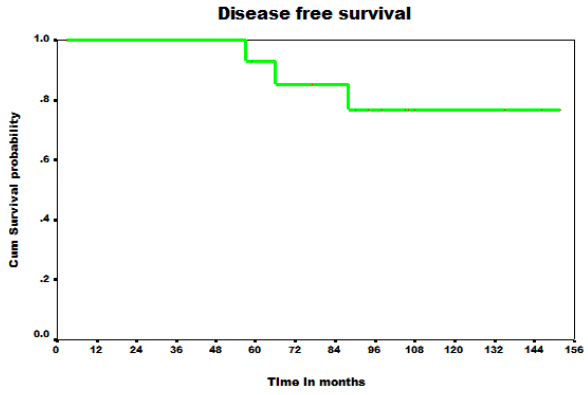


Figure 2. Disease-free survival of mediastinal germ-cell tumour



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