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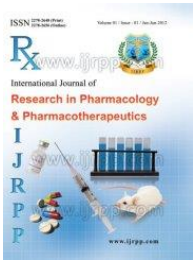

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A prospective study on the efficacy of two drug combination chemotherapy in patients with malignant gonadal germ cell TUMORS

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ABSTRACT

Malignant gonadal germ cell tumors are the rare malignant tumors which occurs in young individuals at the peak of their reproductive life between 18- 45yrs. Germ cell tumors are sensitive to chemotherapy as well as radiotherapy . Three and four drugs regimen increases the survival of 80-90% with increased drug induced toxicity. This study is to find out the efficacy of two drug regimen with cisplatin and etoposide response in malignant gonadal germ cell tumor . The study was carried out in a tertiary care hospital for a period of 21 months. Twenty six patients were selected and six patients were excluded. Prior to treatment all patients were evaluated with basic investigations. αFP and β HCG levels were estimated before and after chemotherapy. Cisplatin 20mg /m² and Etoposide 75mg/m² was given daily for five consecutive days at an interval of 21 days in four cycles. Patients were observed for adverse effects during the course of therapy. Response was evaluated by evidence of regression of the documented tumors and measuring serum tumor markers level . In this study 85% of patients were complete responders and side effects also less during treatment and the follow up period. 5% were partial responders and 10% were non responders. Partial and non responders were recommended for an alternative therapy.

Keywords: α FP, β HCG

INTRODUCTION

Germ cell tumors are rare malignant neoplasm and account for about 1% of cancers [1]. They are the commonest malignant tumors in the age group of 15 – 45 years. They classified into gonadal and non gonadal germ cell tumors. Gonadal germ cell tumors include both testicular and ovarian germ cell tumors.

Germ cell tumors are associated with two tumors markers: alpha fetoprotein (AFP) and beta human chorionic gonadotropin(B HCG). The levels of these two serum tumor marker are linked to the volume of metastatic disease and thus provide reliable information about the prognosis of treatment [2]. Early germ cell tumors can be treated with radiotherapy and surgery. When the neoplasm is locally advanced or when there is lymph node metastasis it requires surgery followed by chemotherapy. In the early 1960s, germ cell tumors were treated with a single drug, usually vinblastin

alone. This agent was able to induce complete remission in 4 of 30 treated patients [3]. Subsequently combination regimens , Cisplatin, Vinblastin and bleomycin (PVB) and Cisplatin, Vinblastin, bleomycin, dactinomycin and cyclo phosphamide (VAB-6) were introduced. These combinations improved the survival of 80 -90% of the treated patients [4].

The present study aims at evaluating the efficacy of this two drug regimen (Cisplatin and etoposide) in patients with both testicular and ovarian germ cell tumors. The effects were correlated with serum tumor marker levels and also by the evidence of distant metastasis.

MATERIALS AND METHODS

The study was carried out in the Department of Medical Oncology, Government Rajaji Hospital, Madurai, after obtaining approval from the Institutional ethics committee and with the informed consent of the patients.

Only those patients with histopathlogically confirmed malignant gonadal germ cell tumor with either measurable disease after primary surgery or loco regionally advanced disease with or without distant metastasis were included in this study.

Extensive prior treatment with several chemotherapy regimens (Since these patients might have had recurrent relapses),Performance status score of 60 or less in the karnofsky performance status scoring system , impaired renal or hepatic function, Impaired bone marrow function with anemia (Hb<9gm), leucopenia (WBC<4,000) and thrombocytopenia (platelets < 1,00,000) and known allergy/drug intolerance were excluded from the study.

Twenty six patients were selected , due to irregular follow up six patients were excluded from this study. The selected patients were evaluated for performance status, presence or absence of organ dysfunction. History and Clinical evaluation done thoroughly. They were all investigated for complete hemogram , urinary bile pigments, urea, creatinine, fasting blood glucose, serum bilirubin, SGOT, SGPT and serum alkaline phosphatase. Chest X ray PA view, Ultrasonography of abdomen and pelvis and serum tumor markers βHCG and α FP done routinely. CT scan of thorax, abdomen and brain done if indicated by symptoms and signs.

All the selected patients were given cisplatin ($20mg/m^2$) dissolved in 1 pint of 5 percent dextrose. It was given as slow intravenous influsion for 3 hours. This was immediately followed by infusion of etoposide ($75mg/m^2$) dissolved in 1 pint of normal saline and was given as saline intravenous infusion. They were given Inj.Dexamethasone 16mg IV and Inj. Ondansetron 8mg IV 8^{th} hrly to prevent vomiting and hypersensitive reactions. On the day of administration the patients were carefully observed for adverse effects. During the 15 days interval between two successive cycles, patients were discharged and permitted to stay at home. They were instructed to report any adverse events immediately, particularly the occurence of fever, diarrhoea, dysentery, oral ulcers, jaundice and breathlessness.

The response to treatment with cisplatin and etoposide combination was evaluated by evidence of regression of the documented tumors as revealed by ultrasonography, chest x-ray and other imaging modalities as recorded and estimating the tumor markers α FP and B HCG before 1^{st} cycle and at the end of the 4^{th} cycle. The response to chemotherapy is quantified as complete response, partial response and no response .

Complete response was defined as the disappearance of all clinical, radiological and biochemical evidence of disease for at least 4 weeks . this includes patients whom residual masses were completely resected by surgery after induction chemotherapy . partial response was defined as 50% reduction of the measurable disease with elevated tumor markers. Non response was defined as 25% increase in the measurable disease.

At the end 4^{th} cycle complete responders were reevaluated and discontinued from the treatment. Partial and non responders were offered an alternative treatment.

RESULTS

20 patients with various forms of gonadal germ cell tumors were enrolled in this study

Table-1: various types of germ cell tumors

Malignant gonadal germ cell tumors	Number of patients
Testicular germ cell tumor	
Seminoma	4
Embryonal carcinoma	1
Malignant teratoma	1
Yolk sac tumor	1
Mixed germ cell tumor	3
Ovarian germ cell tumor	
Dysgerminoma	2
Malignant teratoma	2
Endodermal Sinus tumor	3
Mixed germ cell tumor	3

In seminoma and dysgerminoma, the tumor markers are usually absent due to the absence of trophoblast, were evaluated directly by the measured regression of the initially documented tumor masses or secondaries in the para aortic lymphnode /liver/ lungs as appropriate.

The nonseminomatous and nondysgerminomatous tumors, tumor markers (αFP and βHCG) are often secreted and are measurable in the serum. Hence the response to chemotherapy can be evaluated in these tumors indirectly by estimating the serum tumors markers, as also directly by the measured regression of initially documented tumor masses.

MARKER STATUS AT PRESENTATION

Table 2. Testicular germ cell tumors - Marker status

Tumor	Number			
		I	II	III
Seminoma	4	0/4	3/4 AFP (-) HCG (-)	¼ AFP (-) HCG (-)
Embryonal Carcinoma	1	0/1	1/1 AFP>529 HCG<200	0/1
Malignant Teratoma	1	0/1	1/1 AFP<200 HCG<200	0/1
Yolk Sac Tumor	1	0/1	0/1	1/1 AFP>529
Mixed germ Cell tumor	3	0/3	0/3	3/3 AFP<200-2 >529 -1 HCG<200 -1 >653 -2

Table – 3: Ovarian germ cell tumors-marker status

Tumor	Number	Stage			
		I	II	III	IV
Dysgerminoma	2	0/2	2/2 AFP (-) HCG (-)	0/2	0/2
Malignant Teratoma	2	0/2	2/2 AFP<200-1 <529-1 HCG<200-1 <400-1	0/2	0/2
Yolk Sac Tumor	3	0/3	2/3 AFP<400-1 <529-1	1/3 AFP<400-1	0/3
Mixed germ cell	3	0/3	1/3 AFP<529-1 HCG<200-1	2/3 AFP<529-1 >529-1 HCG>200-1 >400-1	0/3

Serum tumor markers (AFP, HCG) level were estimated before and after chemotherapy in non seminomatous and nondysgerminomatous tumors . After chemotherapy the serum markers level reduced significantly ($P < 0.05$)

Non responders the tumor marker level reduced partially. The results are depicted in figures 1&2.

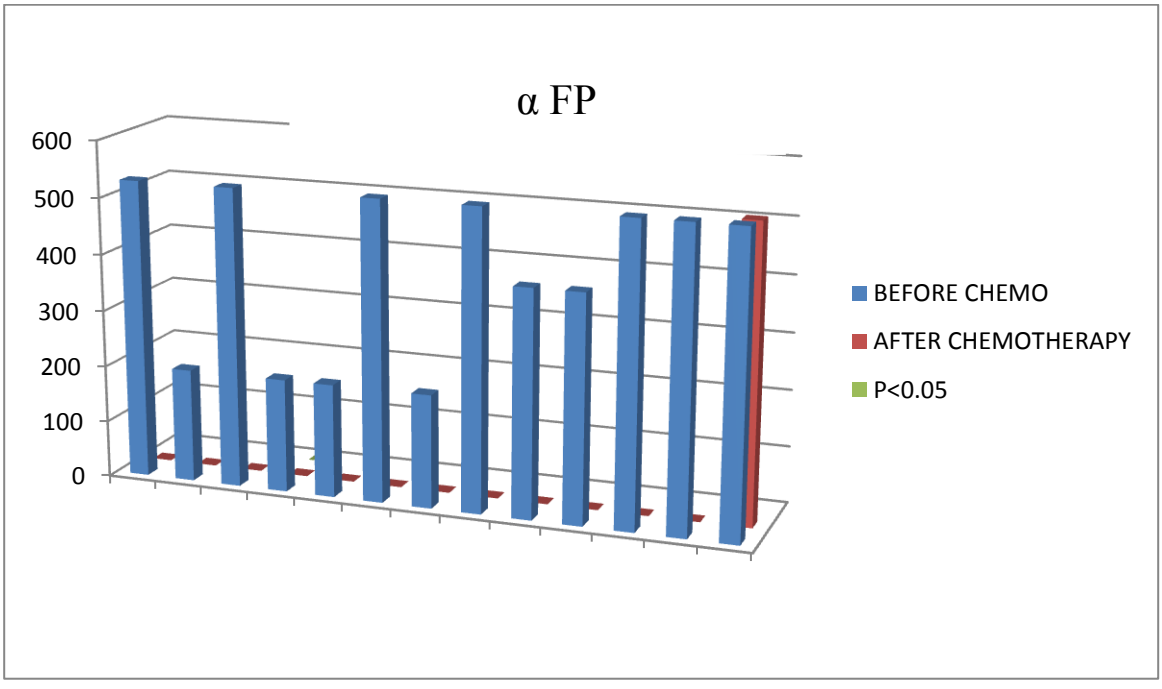

Fig.1 Alpha Fetoprotein

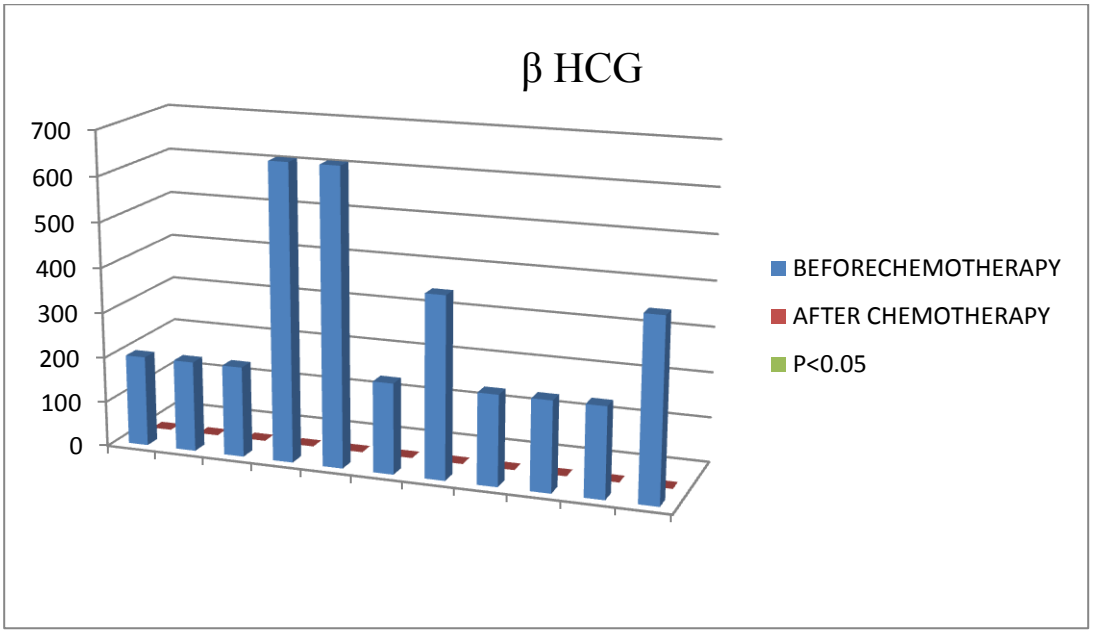

Fig 2. Beta hcg

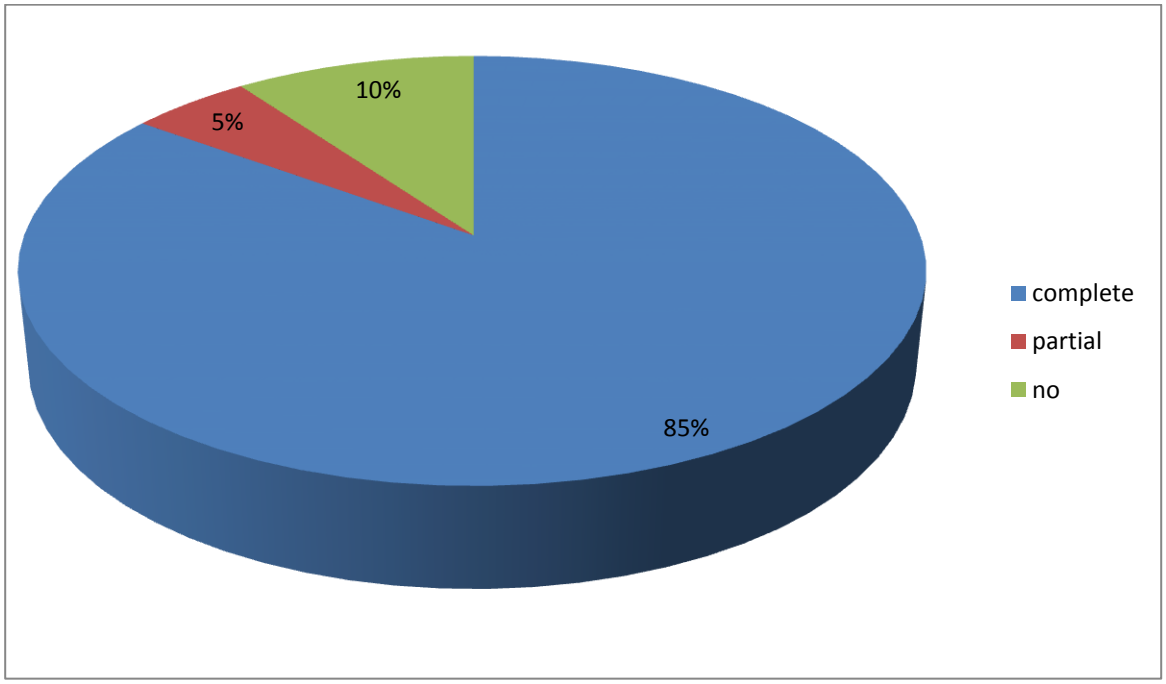

Fig.3 Total Response to Chemotherapy

85% of patients were responded well to the treatment and there was no significant side effects during the follow up period. Partial responders and non responders were offered an alternative chemotherapy regimen.

Toxicity Profile

Total Cycles administrated 80

Absolute neutrophil Count < 1000 at the end of Chemotherapy cycle 0/80

Adverse effects	Results
Nadir neutropenia	< 1000 7/80 <50 0/80
Nadir thrombocytopenia	<50,000 2/80, <20000 0/80
Nausea/ Vomiting	Mild 63/80
	Moderate 12/80
	Severe 5/80
Mucositis	Gr I 7/80
	Gr II 0/80
	Gr III/IV 0/80
Total Alopecia	100%
Hyper pigmentation	palms & nails 100%
Tetany	0
Arterial Occlusion	0
Peripheral neuropathy	3/20 (15%)

There was no chemotherapy related mortality reported during the study period.

DISCUSSION

Germ cell tumors are highly curable neoplasms. Early detection and treatment results in 5 year disease free survival of greater than 95% and also preserves fertility which is an important issue for an young individual [6]. Combination chemotherapy increases the drug related toxicity. In the present study, combination of cisplatin and etoposide is most often preferred for the first line treatment of malignant germ cell tumors of testis and ovary. This combination is less toxic, but at the same time does not diminish the response rate and survival duration.

World wide many randomized clinical trials on cisplatin and etoposide combination chemotherapy have been conducted in patients with malignant gonadal germ cell tumors. The reports revealed complete response rate of 88-93% in patients with stage 1 and stage II [7, 8, 9, 10]. Hence cisplatin and etoposide combination chemotherapy has been accepted as a standard regimen for stage I and stage II malignant testicular germ cell tumors.

Regarding ovarian germ cell tumors, the the incidence is very rare. The occurrence of ovarian germ cell tumor is only one tenth of testicular germ cell tumors. Because of the rarity, randomized studies have not been conducted in ovarian germ cell tumors. Chemotherapy trials results obtained from testicular germ cell tumors have been applied to the ovarian germ cell tumors [11, 12, 13].

In the present study complete responders were on regular follow up, there was no evidence of relapse during the mean follow up period of 8 months. Partial responders were recommended for an alternative therapy. Non responders were stage III patients with distant metastasis. Post chemotherapy evaluation in these patients revealed marked elevation of the tumor markers and progression of distant metastasis. These patients were also offered for four drug combination chemotherapy.

CONCLUSION

Malignant gonadal germ cell tumors are highly curable neoplasm in early stage. They commonly occurs in young individuals at their peak of reproductive age. Recently the incidence is found to increased in developed countries and also in HIV positive men [14]. These factors focus the early detection and management of malignant gonadal germ cell tumors. Our study also revealed high response rate in stage I and stage II with less drug induced toxicity. The efficacy is almost equal with trails conducted earlier. However our study needs long term follow up to find out the occurrence of relapse and disease free survival.

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