Regression Pattern of Alpha Fetoprotein Level Changed after Treatment of Malignant Germ Cell Tumor

Sukumarn Sanersak MD*,
Nisa Prueksritanond MD**

** Fellowship in Gynecologic Oncology, Department of Obstetrics and Gynecology Rajavithi Hospital, Bangkok*
*** Gynecologic Oncologist, Department of Obstetrics and Gynecology Rajavithi Hospital, College of Medicine, Randsit University, Bangkok*

Objective: *To identify the regression pattern of serum alpha fetoprotein in malignant germ cell tumors after initial chemotherapy.*
Material and Method: *This was a retrospective descriptive study. All patients with malignant germ cell tumor who had elevated serum alpha fetoprotein (AFP) and received adjuvant chemotherapy in Rajavithi Hospital between January 1984 and May 2007 were included.*
Results: *Sixty patients with malignant germ cell tumor that met the study criteria were included. The median progression free interval (PFI) was 64.3 months and the median overall survival (OS) was 70.9 months. Four courses of chemotherapy was the average. AFP was first negative after a mean of course of three. Two more cycles were given as a maintenance course. The regression of AFP, between its level before the first and second courses was less than 0.015, associated with survival, accuracy about 70%, sensitivity 83.3%. The number of maintenance courses of chemotherapy was statistically affected to PFI and OS (p-value of 0.025, 0.003, respectively).*
Conclusion: *The regression of AFP is an independent prognostic factor in malignant germ cell tumor and may be a useful tool in the therapeutic management of these patients.*

Keywords: *Progression free interval, Serum alpha fetoprotein, Malignant germ cell tumor*

J Med Assoc Thai 2008; 91 (3): 287-94
Full text. e-Journal: *http://www.medassocthai.org/journal*

The malignant germ cell tumor is estimated to be 5-12% of malignant ovarian tumors[1,2]. In Thailand, it is reported to be about 6.6%[3]. The recent National Comprehensive Cancer Network Clinical Practice Guidelines in management of malignant germ cell tumor recommends initial surgical staging followed by adjuvant treatment. In the past, some guidelines suggested radiotherapy as adjuvant because the germ cell tumor is radiosensitive. However, it may destroy ovarian function in conservative surgical staging cases. Nowadays, adjuvant chemotherapy is given to all patients with malignant germ cell tumor except dysgerminoma stage Ia and immature teratoma stage Ia. Many malignant germ cell tumors have tumor markers. Endodermal sinus tumor usually has elevated serum alpha fetoprotein level and choriocarcinoma has elevated serum human chorionic gonadotopin level. The tumor marker is a useful tool to follow up the disease, because if the tumor marker is elevated, it represents residual disease, and if it decreases, it means that the disease may respond to the treatment[4].

Serum level of alpha fetoprotein is elevated in approximately 80% of patients with disseminated non-seminoma germ cell tumors[5]. Tumor marker normalization is one of the primary objectives to reach patients receiving primary chemotherapy, and the lack of normalization is often associated with an incomplete response. Limitation of some studies include small number of subjects and difficulty due to variety of methods used for the calculations of tumor marker

Correspondence to : Sanersak S, Department of Obstetrics and Gynecology, Rajavithi Hospital, Rajavithi Rd, Rajthevee, Bangkok 10400, Thailand. E-mail: ssanersak @yahoo.com

decline rates, and tumor marker determinations performed relatively late after the start of chemotherapy (which may allow only a late treatment switch).

Therefore, the authors assessed whether the decline rate of serum alpha fetoprotein may be correlated with progression free interval and overall survival in malignant germ cell tumor.

Material and Method

This was a retrospective descriptive study. All patients with malignant germ cell tumor who had elevated serum alpha fetoprotein and received adjuvant chemotherapy in Rajavithi Hospital from January 1984 to May 2007 were included. The present study was approved by the Ethics Committee of Rajavithi Hospital.

The patients' clinical and pathological data were collected from the medical records and included tumor charts and follow-up information. As of May 31, 2007, sixty-five patients with histology confirmed malignant germ cell tumor and elevated serum alpha fetoprotein, were identified. The patients' age, staging according to the 1987 International Federation of Obstetrics and Gynecology(FIGO) staging system[6], histological types(from record in office histological report) and total cycles of adjuvant chemotherapy received and serum alpha fetoprotein level were collected. The date of first diagnosis of malignant germ cell tumor, the date of each course of chemotherapy, the date of recurrence, the date of last visit and the date of death were all recorded. The negative level of serum alpha fetoprotein (AFP) used in Rajavithi Hospital was less than or equal to 5 mg/ml.

The inclusion criteria were patients with malignant germ cell tumor who had elevated serum alpha fetoprotein that had surgery followed by adjuvant chemotherapy. The main outcome was progression free interval and overall survival.

Follow up examination took place at the Gynecologic Oncology Unit. Patients were scheduled for follow up every 2 months in the first year, every 3 months during the second year and every 6 months thereafter. Follow up data, such as date of last visit and disease status at the time of the last contact were noted. All patients were followed until date of death or lost to follow up.

The progression free interval (PFI) was defined as time from the date of diagnosis to the date of disease progression (as specified by clinical or radiological or surgical evidence of relapse or elevated serum alpha fetoprotein level) or to the date of last follow up in cases without progression. The overall survival (OS) was defined from the date of primary laparotomy to the date of death or the date of last follow up[7]. The maintenance course was defined as additive number of chemotherapeutic course after serum AFP become negative.

The statistical analysis was done using the Statistical Package for the Social Sciences (SPSS) and the descriptive statistics were used for demographic data and summarized as mean, median and standard deviation (SD)for progression free interval and overall survival, variation between patients use ANOVA method. Survival curves were estimated by the Kaplan-Meier method and compared using the log-rank test in univariate analysis. A p-value of less than 0.05 was considered statistically significant. The sensitivity data for predicting death was done by use of ROC curve (received operational curve).

Results

From January 1984 to May 2007, 65 cases of malignant germ cell tumor that had elevated AFP were registered in the gynecologic oncology unit of Rajavithi Hospital. The total cases enrolled in the present study were 60 because five cases had not received complete treatment and had no available data for evaluation.

The patients' characteristics are shown in Table 1. The mean time to follow up was 68.3 months, range 1.3 to 243 months. The mean age of patients was 24 years with the range of 10 to 53 years.

Stage and cell types are shown in Table 1. Most of the patients were in stage Ic and IIIc, 31.7% and 25%, respectively. Most common histological cell types that had elevated AFP were endodermal sinus tumor (71.7%) and mixed tumor (20%). Mixed tumor group consisted of 2 cases of EST with immature teratoma, 2 cases of EST with embryonal carcinoma, 3 cases of EST with dysgerminoma, and one case each of EST with mucinous carcinoma, EST with dermoid, EST with dysgerminoma and embryonal carcinoma, embryonal carcinoma with choriocarcinoma and dysgerminoma with polyembryonal carcinoma.

The data on chemotherapy regimens is shown in Table 1. The combination chemotherapy regimens given in malignant germ cell tumor after surgery were BEP regimen (combination of bleomycin, etoposide and cisplatin) in 40 patients (66.7%), VAC regimen (combination of vinblastine, actinomycin and cyclophosphamide) (this regimen was generally used before 1996) in 16 patients (26.7%), and other regimens

Table 1. Base line characteristics of patients (total n = 60)

Characteristics	n	Percent (%)
Age (yr)	Mean 24.02	Range 10-53
Occupation		
Employee	13	21.7
Housewife	8	13.3
Farmer	5	8.3
Government	1	1.7
Other	13	21.7
No data	20	33.3
Marital status		
Single	36	60.0
Married	16	26.7
Divorce	2	3.3
No data	6	10
Stage		
Ia	13	21.7
Ib	1	1.7
Ic	19	31.7
IIa	1	1.7
IIb	2	3.3
IIc	2	3.3
IIIa	4	6.7
IIIb	2	3.3
IIIc	15	25.0
IV	1	1.7
Cell type		
Endodermal sinus tumor	43	71.7
Dysgerminoma	1	1.7
Embryonal carcinoma	1	1.7
Immature teratoma	3	5.0
Mixed tumor	12	20.0
Regimen		
BEP	40	66.7
VAC	16	26.7
Other		
PVB	2	3.3
Platinum combination	2	3.3

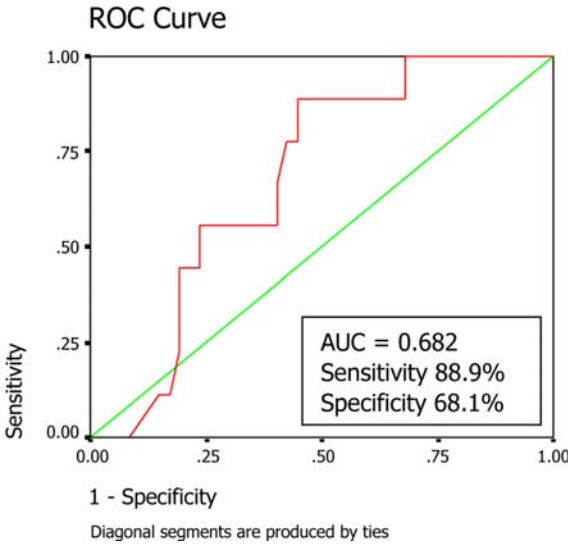

Fig. 1 ROC curve for AFP level before first course of chemotherapy in predicting mortality (the optimal cut off point with the highest sensitivity and specificity for survival)

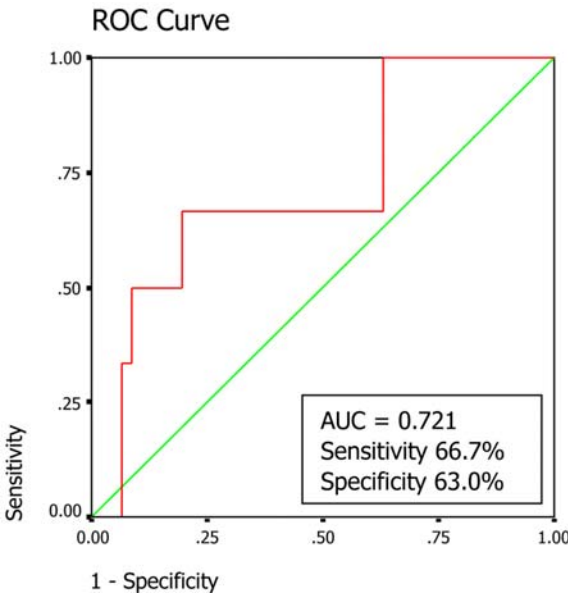

Fig. 2 ROC curve for AFP level before second course of chemotherapy in predicting mortality (The optimal cut off point with the highest sensitivity and specificity for survival)

such as PVB (combination of platinum, vincristine, bleomycin) in two patients (3.3%) and platinum base combination in two patients (3.3%). Of the two patients that received platinum based combination, one patient had received combination of cisplatin and cyclophosphamide for two courses and changed to BEP regimen for four courses and the other one had received intraperitoneal cisplatin plus VAC regimen for four courses.

The total number of adjuvant chemotherapeutic courses given in most was four or six courses, 25.0% and 21.7%, respectively. Mean and median were three and four courses each with an average of one to seven courses. The mean number of courses of chemotherapy at which AFP level become first negative was three courses (range 2-6). The maintenance course of

chemotherapy given in most was two courses (about 33.3%) (range 0-4 courses).

The mean AFP level before the first course of chemotherapy was 9567.44 mg/ml, range 25-56200 mg/ml. The AFP levels before the second course of chemotherapy in most cases decreased with mean level 1220.2 mg/ml, range 0-20000 mg/ml. AFP level was able to predict death by using the ROC curve. If AFP level before the first course of chemotherapy was 497.6 mg/ml it predicted death with accuracy of 68.2%, sensitivity 88.9%, specificity 68.1% (Fig. 1) and AFP level of 47.5 mg/ml before second course of chemotherapy predicted death with accuracy of 72.1%,sensitivity 66.7%, specificity 63.0%, Fig. 2. Regression of AFP before the second course of chemotherapy (C2) compared with AFP level before the first course of chemotherapy (C1) if divided (C2/C1) and found to be more than 0.015 can predict death with the highest accuracy of 68.5%, sensitivity 83.3% and specificity 68.9%, Fig. 3. Difference in value of AFP from this period was analyzed in a survival curve and found to be statistically significant in OS, p = 0.03 (Fig. 4).

The survival analysis was performed in 49 patients with follow-up of more than 36 months and available recent status. The 5-year survival was 68%. The survival of patients, when analyzed by subgroups in favorable group (regression of AFP between first and second course less than 0.015 or equal)and unfavorable group (regression of AFP between first and second course more than 0.015) was found that 3-year survival were 79.3% and 60.9%, respectively and 5-year survival were 74.0% and 48.5% respectively. The data of subgroup analysis did not have a difference in baseline characteristics between the groups.

The median PFI was 64.3 months, range 0.6 to 255.3 months. The disease after complete surgery and chemotherapy, recurred in eight patients (15%), see Table 2. The median OS was 70.9 months, range 0.6 to 255.3 months.

In subgroup analysis, PFI was found to be longer if AFP became negative after fewer chemotherapy courses but when analyzed by SPSS program and calculated by the ANOVA method, it was not found to be statistically significant, p = 0.424.

The PFI is compared between less than two maintenance courses vs. more than two and it was more prolonged if the maintenance course was more than two, which was statistically significant, p = 0.025. The OS was also decreased in patients who received less than two maintenance chemotherapy, statistically significant, p = 0.003, see Fig. 5-6.

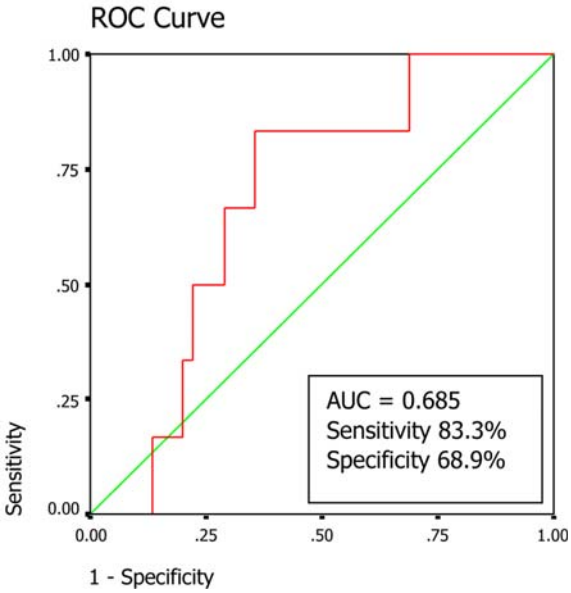

Fig. 3 ROC curve for regression of AFP level before first and second course of chemotherapy in predicting mortality (the optimal cut off point with the highest sensitivity and specificity for survival)

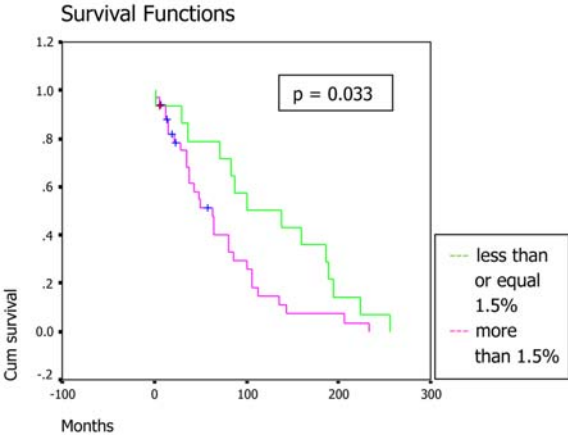

Fig. 4 Overall survival according to regression rate of AFP level between before first and second course of chemotherapy (less than or equal 1.5% versus more than 1.5%) (n = 49)

Discussion

In the present study, the authors evaluated AFP in regression pattern between its level before the first and before the second course of adjuvant chemotherapy in malignant germ cell tumor. The authors found that if regression of AFP level in this period is

Table 2. Data in recurrence group

Age (year)	Stage	Cell type	Chemotherapeutic type	Chemotherapeutic courses	PFI (Mn)	OS (Mn)
31	Ic	EST	BEP	6	12.1	13.8
32	IV	EST	EP	5	8.8	18.6
16	IIIc	EST	VAC	4	9.1	138.7
17	Ic	EST+immature	VAC	4	9.1	58.0
27	Ia	EST+dysgerm	VAC	3	21.3	186.9
34	Ic	EST	BEP	5	8.3	11.8
35	Ib	EST	BEP	6	15.3	26.2
27	IIIc	EST	EP	6	4.6	23.2

EST; endodermal sinus tumor, Immature; immature teratoma, dysgerm; dysgerminoma, PFI; progression free interval, OS; overall survival, Mn; months

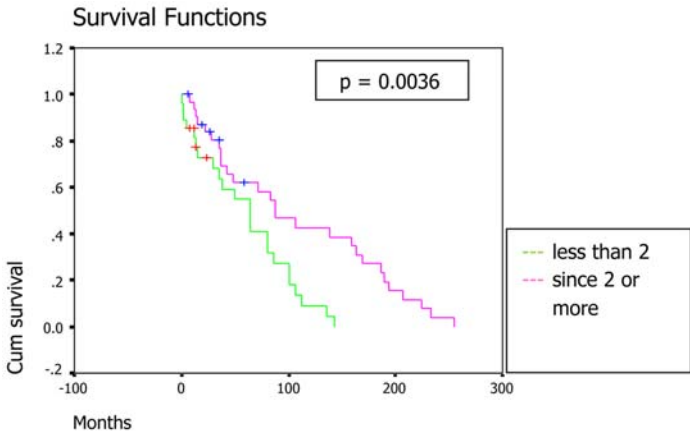

Fig. 5 Overall survival according to maintenance course after AFP negative (less than 2 versus since 2 courses or more) (n = 60)

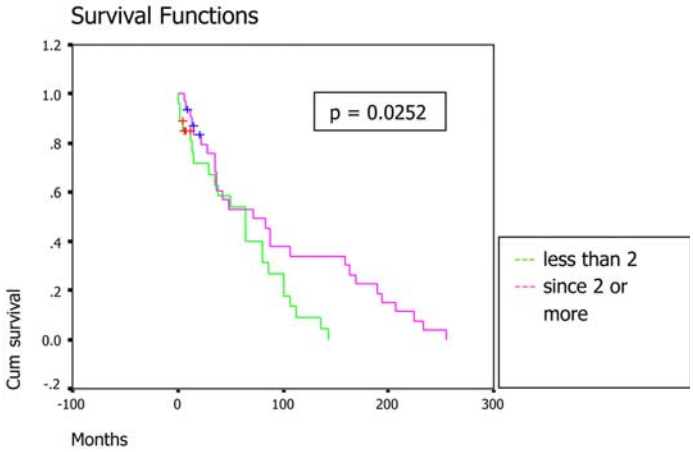

Fig. 6 Progression free interval according to maintenance course after AFP negative (less than 2 versus since 2 courses or more) (n = 60)

less than 1.5%, accuracy to predict death is about 70%, It means that AFP level should decrease a lot between this period. The regression pattern of AFP may be a useful tool in the therapeutic management of malignant germ cell tumor. This regression pattern was calculated by using the maximum area under the curve in ROC curve. The presented data is not similar to other studies[4,7-11]. Karim et al[7] reported the outcome in nonseminomatous germ cell tumors, when using the predicted time to normalization of tumor marker by calculation in the logarithmic transformation formula. Steven et al[9] reported regression rates of the serum tumor marker in testicular teratoma was calculated from the half-life formula. They concluded that early evaluation of the tumor marker half-life formula does not predict patients at higher risk and is a poor guide to long-term prognosis. It is not like the present study formula, it can predict survival. The other studies[4,11] identified the definite time, serum AFP levels should return to normal within 5-8 weeks following complete tumor excision or radiation therapy that predicted outcome. This data is not similar to other tumor markers in germ cell tumors such as serum HCG level. Serum HCG level was calculated using a logarithmic transformation data to predict survival[12]. Although serum HCG level correlated well with response of disease to chemotherapy, it can predict survival only in choriocarcinoma[12,13]. The present data does not correlate to half-life of AFP and if used by other formula for calculation such as logarithmic transformation like HCG or diminished in two values not found more than accuracy in this method.

Alpha fetoprotein is a glycoprotein with MW ranging from 61000-71000 dalton[4], produced from fetal yolk sac and elevated in malignant germ cell tumors. AFP level is the prognostic factor in malignant germ cell tumor[14,15]. The normal value of serum alpha fetoprotein level depends on individual laboratory institute but in the present study the cutoff point used was less than 5 mg/ml. Histological subtypes of malignant germ cell tumor that have elevated serum AFP level are 100% of endodermal sinus tumor and 33% of immature teratoma[16].

In general, following treatment guidelines, AFP level was checked before every course of chemotherapy and at every visit to predict complete treatment or diagnose refractory disease. AFP level before the first course of chemotherapy in the present study ranged 25-56200 mg/ml, AFP in this period was calculated by ROC curve for predicted death was found if more than 497.6 mg/ml have an accuracy of 68.2%. After the first course of chemotherapy, the AFP level was evaluated before the second courses and range in the present study was 0-20000 mg/ml. The level before the second course of chemotherapy, of more than 47.5 mg/ml can predict death with accuracy of 72.1%. This data shows if AFP level is high it inversely reflected the survival of patients and they should be given intensive chemotherapy treatment and close follow up. Tsuchida et al[17] confirmed these findings in endodermal sinus tumors and reported that the production rate of AFP closely correlated with the amount of viable malignant tumor tissue.

Malignant germ cell tumor is mostly found in young patients. From the present study, mean age was 24 years, which is similar to other data[14,15]. Regarding surgical treatment, some patients were treated by conservative surgery so that if they were cured, the patients could conceive. In the present study, there was no difference in survival between patients receiving conservative and more radical surgery. After surgery, many patients with malignant germ cell tumor received adjuvant chemotherapy except dysgerminoma stage IaG1 and immature teratoma stage IaG1. The present study included one patient with dysgerminoma, stage IIB, who had elevated AFP level and three patients of immature teratoma, all in stage IIIC with elevated AFP level. On evaluation of histologic type and prognosis of malignant germ cell tumor in the present study, there was no statistically significant difference in PFI and OS between EST and non-EST group.

In treatment of malignant germ cell tumor, multiple chemotherapeutic regimens were used. In the past, the first line was VAC; after that, new recommendation is BEP, because previous studies showed effectiveness of BEP regimen to be more than that of VAC with less adverse effects from chemotherapy. In the present study, twenty-six percent of patients received VAC regimen. Most of these groups were treated before 1996 after which the regimen was changed to BEP. Data from the present study shows survival difference between the regimens to be statistically significant both in PFI and OS.

After chemotherapy, the present study shows that mean course of first negative AFP level was three courses and the early time to normalization of AFP level had a better prognosis. However, more than two maintenance courses given had a statistically significant effect on PFI and OS with P 0.025 and 0.03, respectively. Although, in the literature, the authors suggest a maintenance course of chemotherapy 1-2, data in the present study recommended at least two courses.

Conclusion

The regression of AFP is an independent prognostic factor in malignant germ cell tumors and may be a useful tool in the therapeutic management of these patients.

Acknowledgements

The authors want to thank Kitiphong Harncharoen, Ph.D. as the statistical consultant and Dr. Ugen Tshomo for editing the manuscript.

References

1. American College of Obstetricians and Gynecologists. In: DiSaia PJ, editor. Precis V: An update in obstetrics and gynecology. Washington DC: ACOG; 1994: 326-7
2. Creasman WT, Soper JT. Assessment of the contemporary management of germ cell malignancies of the ovary. Am J Obstet Gynecol 1985; 153: 828-34.
3. Vilailak S. In: Vilailak S, editor. Cancer of ovary: ovarian germ cell tumor. Bangkok: Beyond Enterprises; 2005: 54-78.
4. Donaldson ES, van NJ Jr, Gay EC, Purcell S, Meeker WR, Kashmiri R, et al. alpha-Fetoprotein as a biochemical marker in patients with gynecologic malignancy. Gynecol Oncol 1979; 7: 18-24.
5. Bosl GJ. Circulating tumor markers: biologic markers of malignancies. In: MacDonald JS, Haller DG, Mayer RJ, editors. Manual of oncologic therapeutics. 3rd ed. Philadelphia: Lippincott; 1995: 49-54.
6. DiSaia PJ, Creasman WT. Clinical gynecologic oncology: epithelial ovarian cancer. 6th ed. St. Louis: Mosby; 2002: 289-624.
7. Fizazi K, Culine S, Kramar A, Amato RJ, Bouzy J, Chen I, et al. Early predicted time to normalization of tumor markers predicts outcome in poor-prognosis nonseminomatous germ cell tumors. J Clin Oncol 2004; 22: 3868-76.
8. Mazumdar M, Bajorin DF, Bacik J, Higgins G, Motzer RJ, Bosl GJ. Predicting outcome to chemotherapy in patients with germ cell tumors: the value of the rate of decline of human chorionic gonadotrophin and alpha-fetoprotein during therapy. J Clin Oncol 2001; 19: 2534-41.
9. Stevens MJ, Norman AR, Dearnaley DP, Horwich A. Prognostic significance of early serum tumor marker half-life in metastatic testicular teratoma. J Clin Oncol 1995; 13: 87-92.
10. Schmoll HJ, Beyer J. Prognostic factors in metastatic germ cell tumors. Semin Oncol 1998; 25: 174-85.
11. Talerman A, Haije WG, Baggerman L. Serum alphafetoprotein (AFP) in diagnosis and management of endodermal sinus (yolk sac) tumor and mixed germ cell tumor of the ovary. Cancer 1978; 41: 272-8.
12. Lertkhachonsuk R, Limpongsanurak S. Serum human chorionic gonadotropin regression pattern in persistent trophoblastic disease during chemotherapy. J Med Assoc Thai 2001; 84(Suppl 1): S352-9.
13. Picozzi VJ Jr, Freiha FS, Hannigan JF Jr, Torti FM. Prognostic significance of a decline in serum human chorionic gonadotropin levels after initial chemotherapy for advanced germ-cell carcinoma. Ann Intern Med 1984; 100: 183-6.
14. Nawa A, Obata N, Kikkawa F, Kawai M, Nagasaka T, Goto S, et al. Prognostic factors of patients with yolk sac tumors of the ovary. Am J Obstet Gynecol 2001; 184: 1182-8.
15. Kramar A, Droz JP, Rey A, Bouzy J, Philippot I, Culine S. Prognostic factors in non-seminomatous germ cell tumours of the testis. Experience at the Institut Gustave-Roussy. Eur Urol 1993; 23: 188-95.
16. Ihara T, Ohama K, Satoh H, Fujii T, Nomura K, Fujiwara A. Histologic grade and karyotype of immature teratoma of the ovary. Cancer 1984; 54: 2988-94.
17. Tsuchida Y, Saito S, Ishida M, Omi K, Urano Y. Yolk sac tumor (endodermal sinus tumor) and alpha-fetoprotein. A report of three cases. Cancer 1973; 32: 917-21.

รูปแบบการลดลงของระดับอัลฟาฟีโตโปรตีนหลังจากได้รับการรักษามะเร็งรังไข่ชนิดเจอร์มเซลล์

สุขุมาลย์ เสนอศักดิ์, นิสา พฤกษะริตานนท์

วัตถุประสงค์: *เพื่อสืบค้นรูปแบบการลดลงของระดับอัลฟาฟีโตโปรตีนของมะเร็งรังไข่ชนิดเจอร์มเซลล์หลังจากการได้รับยาเคมีบำบัด*

วัสดุและวิธีการ: *การศึกษาแบบบรรยายย้อนหลัง ผู้ป่วยมะเร็งรังไข่ชนิดเจอร์มเซลล์ทุกคนที่มีการเพิ่มขึ้นของระดับอัลฟาฟีโตโปรตีนในเลือดและได้รับยาเคมีบำบัดที่โรงพยาบาลราชวิถี ในช่วงเดือนมกราคม พ.ศ.2527 ถึงเดือนพฤษภาคม พ.ศ.2550*

ผลการศึกษา: *ผู้ป่วยมะเร็งรังไข่ชนิดเจอร์มเซลล์ในการศึกษานี้จำนวน 60 ราย ค่ากลางของระยะปลอดโรค 64.3 เดือน และระยะมีชีพ 70.9 เดือน จำนวนครั้งของยาเคมีบำบัดทั้งหมดเฉลี่ย 4 ครั้ง จำนวนครั้งของยาเคมีบำบัดที่มีค่าอัลฟาฟีโตโปรตีนเป็นลบเฉลี่ย 3 ครั้ง และจำนวนครั้งของเคมีบำบัดที่ให้เพิ่มเติมเฉลี่ย 2 ครั้ง รูปแบบการลดลงของระดับอัลฟาฟีโตโปรตีนค่าระหว่างก่อนให้ยาเคมีบำบัดครั้งที่ 1 และ 2 น้อยกว่า 0.015 มีความสัมพันธ์ต่ออัตราการมีชีวิตรอดโดยพบความแม่นยำร้อยละ 70 ความไวร้อยละ 83.3 จำนวนครั้งของเคมีบำบัดที่ให้เพิ่มเติม มีผลต่อระยะปลอดโรคและระยะมีชีพอย่างมีนัยสำคัญทางสถิติ P มีค่า 0.025 และ 0.003 ตามลำดับ*

สรุป: *รูปแบบการลดลงของระดับอัลฟาฟีโตโปรตีนเป็นปัจจัยในการพยากรณ์โรคมะเร็งรังไข่ชนิดเจอร์มเซลล์ และเป็นเครื่องมือในการดูแลผู้ป่วยกลุ่มนี้*