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Kinetics of tumor marker decline as an independent prognostic factor in patients with relapsed metastatic germ-cell tumors.

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Early serum tumor marker decline (STMD) during chemotherapy was shown to predict survival in patients with poor prognosis non-seminomatous germ cell tumors (GCT) in the first line. The aim of the study was to assess the prognostic value of STMD in relapsed GCT`s patients. From January 1995 to December 2007, all patients treated for GCT´s with salvage therapy at the National Cancer Institute of Slovakia were identified from the tumor registry database and screened retrospectively for serum AFP and βHCG level at the time of relapse. STMD rate was calculated for each patient and each tumor marker with an abnormal marker value at baseline and each tumor marker M (HCG or AFP) using only two values: the baseline value (M_0) and the value obtained after one cycle of chemotherapy (day 21 value; M_1). The decline rate was calculated using a logarithmic transformation, and it was expressed as a theoretical number of weeks necessary to normalization that was called predicted time to normalization. Decline rates were classified into „favorable" or „unfavorable". Totally, 75 patients were identified, 39 had favourable (group A) and 36 unfavorable (group B) STMD. The 2-year and 5-year PFS rates were 61% and 58% for group A and 17% and 7% group B ($p < 0.00001$). Simillary, the 2-year and 5-year OS rates were 79% and 68% for group A and 24% and 16% for group B ($p < 0.00001$). Of all the baseline characteristics that were included in the Cox model, STMD was the most important predictor of PFS and OS. We suggest that STMD is strong independent prognostic factor in GCT patients treated with salvage chemotherapy. Prospective studies of different approaches in this patient`s population based on STMD are warranted.

Keywords: germ cell cancer; salvage chemotherapy; serum tumor marker decline

Germ cell tumors (GCT) belong to the most chemosensitive solid tumors and represent a model for a curable cancer [1]. Cisplatin represents the mainstay in the treatment of GCTs. Cisplatin-based 1st line chemotherapy can cure about 70%-80% of patients with disseminated testicular cancer [2, 3, 4]. Salvage chemotherapy with standard dose cisplatin plus previously not utilized drugs will cure 20-25% of patients who were not initially cured with their induction chemotherapy [5, 6, 7, 8].

Treatment efficacy strongly correlates with prognostic factors [9]. The first and the most important prognostic factor is complete remission (CR) that is achieved either with primary cisplatin-based chemotherapy only or with cisplatin-based chemotherapy (partial remission) followed with surgical complete removal of all residual tumor masses. Fossa et al. identified three prognostic factors in relapsed germ cell tumors which remain significant in multivariate analysis: progression free interval, CR to induction treatment and the level of serum β-human chorionic gonadotropin (βHCG) and α-fetoprotein (AFP) at relapse. Patients with a progression-free interval of less than 2 years, less than CR to induction chemotherapy and high markers at relapse (AFP > 100 kU/l, βHCG > 100 IU/l) formed a poor-prognosis group [10]. Motzer in an earlier report identified CR to induction therapy, testis primary site and normal serum βHCG and LDH as favourable prognostic factors [2].

Early serum tumor marker decline during chemotherapy was previously shown to predict survival in patients with poor prognosis of disseminated non-seminomatous GCT in first line [11]. AFP decline during the first 6 weeks of salvage chemotherapy predicts PFS in patients with disseminated GCT. Massard et al showed that high-dose chemotherapy in relapsed germ cell tumors may be beneficial only to selected patients with a favorable AFP decline [12].

The aim of this retrospective study was to assess the prognostic value of the kinetics of tumor marker decline in patients with relapsed disseminated germ-cell tumors treated in a single institution.

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Patients and methods

Patient population. This retrospective study was approved by the Ethics Committee of the National Cancer Institute, Slovakia. From January 1995 to December 2007, all patients treated for GCT´s with salvage therapy at the National Cancer Institute of Slovakia were identified from the tumor registry database and screened retrospectively for serum AFP and βHCG level at the time of relapse.

The eligibility criteria were as follows: evidence of relapsed/progressed disseminated GCT´s treated by conventional dose or high-dose chemotherapy; baseline βHCG and AFP measurement available; βHCG and AFP measurements available after first cycle of salvage chemotherapy (theoretically day 21 value). Baseline tumor markers were typically obtained within one week of initiation of chemoterapy and in the majority of patients on day 1 of chemotherapy. In all patients data regarding age at diagnosis, tumor histology, tumor primary, response to the first line chemotherapy, time to recurrence after the first-line and salvage chemotherapy and/or disease status at last follow-up were collected.

Tumor marker decline was expressed as predicted time to normalization. Briefly, the decline rate was calculated for each patient and each tumor marker with an abnormal marker value at baseline and each tumor marker M (HCG or AFP) using only two values: the baseline value (M_0) and the value obtained after one cycle of chemotherapy (day 21 value; M_1). The decline rate was calculated using a logarithmic transformation, and it was expressed as a theoretical number of weeks necessary to normalization that was called predicted time to normalization (TTN): $TTN_M = 3\,a/b$, with $a = \log(M_0) - \log(M_N)$, $b = \log(M_0) - \log(M_1)$, and M_N, the normal value of each tumor marker M.

Results were then classified into four categories: AI_M, normal tumor marker value at M_0 and M_1; AII_M, elevated M_0 and normal M_1; $AIII_M$, elevated M_0 and TTN_M less than T_M; B_M, elevated M_0 and $TTN_M \geq T_M$ or elevated M_0 and increased value at day 21. Cutoff points were set at $T_{AFP} = 9$ weeks for AFP and at $T_{HCG} = 6$ weeks for HCG as described [11].

A marker decline rate is considered favorable when both HCG and AFP fall into either the AI, AII, or AIII categories (group A). A marker decline is considered unfavorable when either HCG or AFP or both fall into the B category (group B). Similar definitions are considered for a half-life greater than 7 days for AFP and greater than 3.5 days for HCG [11]. In final analysis, dissociated marker decline (e.g. favourable decline of one marker, but unfavourable decline of another) was classified as unfavourable marker decline.

Statistical methodology. The primary study goal was to determine whether kinetics of tumor marker decline in patients with relapsed disseminated germ-cell tumors treated with salvage chemotherapy is a predictor of survival.

Disease progression/recurrence was defined on imaging-based criteria (appearance of new lesions by computed tomography or by positron emission tomography scan imaging) and/or rising of serum markers. PFS was defined as the interval between the day 1 of salvage chemotherapy and the day of progression/recurrence or death, whichever occured first. OS was calculated from the day 1 of salvage chemotherapy until the last day of follow-up or day of death.

Standard Kaplan–Meier methods were used to analyze the survival. Log-rank test was used for comparison between the survival curves. A multivariate Cox proportional hazards model for PFS and OS was employed to assess differences in outcome on the basis of serum tumor marker decline after salvage chemotherapy, including other variables such as tumor primary, histology (seminoma vs. nonseminoma) response to induction treatment, progression free interval, and the level of serum β-human chorionic gonadotropin and α-fetoprotein at relapse. Step-wise regression techniques were used to build multivariate models using a significance level of 0.10 to remain in the model. All P values presented are two-sided, and associations were considered significant if the P value is less or equal to 0.05.

Results

After screening 98 patients from our records, a total of 75 patients satisfied the study eligibility criteria. Reasons for ineligibility were incomplete documentation to exactly asses serum tumor markers decline, response or survival (11 patients), growing teratoma syndrome (3 patients), teratoma with malignant transformation (5 patients), second line chemotherapy administered in other hospital (3 patients), radiotherapy without chemotherapy (1 patient). Characteristics of the patient´s population included in this analysis are outlined in Table 1. All patients received cisplatin-based first-line chemotherapy. All markers were measured in the laboratory of the National Cancer Institute.

Median follow-up for all patients was 20 months (range, 1–184 months). Median follow-up for patients who are alive was 71 months (range, 7-152 months). Favourable marker decline experienced 52% of patients. Progression free survival (PFS) and overall survival (OS) on the basis of serum tumor marker decline is shown in the Figure 1 and 2.

Median PFS was not reached in patients with favourable decline (group A) and was 5 months ($P < 0.00001$; log-rank test) in patients with unfavourable tumor marker decline (group B). Thus, 2-year and 5-year PFS rates were 61% and 58% for group A and 17% and 7% for group B, respectively.

Median OS was not reached in patients with favourable decline (group A) and it was 11 months ($P < 0.00001$; log-rank test) in patients with unfavourable tumor marker decline (group B). Thus, 2-year and 5-year OS rates were 79% and 68% for group A and 24% and 16% for group B, respectively.

Of all the baseline characteristics that were included in the Cox model, serum tumor marker decline was the most important predictor of PFS and OS (Table 2 and 3).

In an exploratory analysis, we further analyzed the impact of AFP and βHCG marker on OS and PFS (Table 4). There were statistically significant differences in OS and PFS regarding the decline of AFP and/or βHCG.

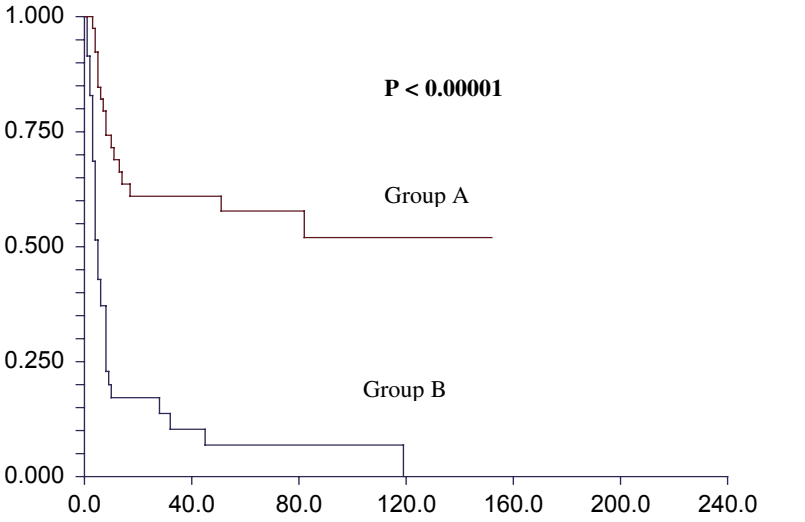
Table 1. Patient characteristics (n= 75)

	No.	%
Median of age (range)	33 years (18 – 57 years)	
Primary tumor		
Gonadal	67	89
Retroperitoneal	6	8
Mediastinal	2	3
Late relapse	14	19
Complete response to 1st line chemotherapy	27	36
Testis primary and complete response to 1st line chemotherapy		
Salvage chemotherapy regimen		
VIP	18	24
TIP	31	41
GCP	9	12
Dose-escalated VIP	4	5
VIP followed by HDCT	3	4
other	10	13
Response to salvage chemotherapy		
favourable (CR+PRnm negat.)	49 (17 + 32)	65 (22 + 44)
unfavourable	26	35
Median progression free survival (95% confidence interval)	8 months (6 – 17 months)	
2-year PFS	40 % (29 % – 51 %)	
5-year PFS	34 % (23 % – 45 %)	
Median overall survival (95% confidence interval)	27 months (16 – 80 months)	
2-year OS	53 % (41 % – 64 %)	
5-year OS	44 % (32 % – 55 %)	
Median (range) of elevated pretreatments markers		
AFP mIU/ml	342 (16 – 45000)	
βHCG IU/ml	344 (8 – 80890)	
Kinetics of serum tumor markers		
AFP		
favourable marker decline	20	45
unfavourable marker decline	25	55
βHCG		
favourable marker decline	15	50
unfavourable marker decline	15	50
Both		
favourable marker decline	39	52
unfavourable marker decline	36	48
Normal baseline tumor markers	14	19

Abbreviations: VIP (etoposide, ifosfamide, cisplatin) , TIP (paclitaxel, ifosfamide, cisplatin), GCP, gemcitabine, paclitaxel, cisplatin), HDCT – high dose chemotherapy with stem cell support

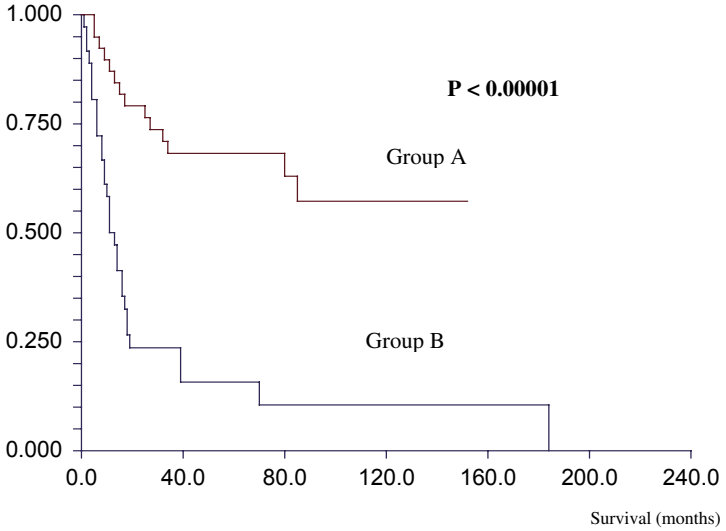
Table 2. Progresion-free survival analysis Cox model

Variable	Relative risk	95% Confidence Interval	p-value
Marker decrease unfavourable vs. favourable	5.51	2.91 – 10.46	< 0.001
Time to progression, months < 24 vs. >24	2.50	1.09 – 5.82	0.030
AFP, mIU/ml + βHCG IU/ml one > 1000 vs. both < 1000	2.29	1.19 – 4.41	0.012



	At Risk	Progression
Group A	22	17
Group B	2	33

Figure 1. Progression free survival on the basis of serum tumor marker decline



	At Risk	Deaths
Group A	25	14
Group B	5	36

Figure 2. Overall survival on the basis of serum tumor marker decline

Table 3. Overall survival analysis Cox model

Variable	Relative risk	95% Confidence Interval	p-value
Marker decrease			
unfavourable vs. favourable	5.39	2.69 – 10.82	< 0.001
Time to progression, months			
< 24 vs. >24	2.33	0.91 – 6.02	0.078
AFP, mIU/ml + βHCG IU/ml			
one > 1000 vs. both < 1000	2.48	1.29 – 4.78	0.006

Table 4. Patients outcome based on serum tumor marker decline

	Progression-free survival *	Overall survival *
AFP	p = 0.0005	p = 0.0024
favourable decline	51 months (8 – 51 months)	80 months (32 – 80 months)
unfavourable decline	4 months (4 – 6 months)	16 months (9 – 18 months)
βHCG	p = 0.002	p = 0.0002
favourable decline	17 months (7 – 17 months)	80 months (17 – 80 months)
unfavourable decline	4 months (2 – 6 months)	6 months (4 –10 months)

* median (95% confidence interval)

Discussion

This retrospective study based on the single centre experience of 75 patients with germ cell tumor, treated with salvage chemotherapy, shows that decline of serum tumor markers (AFP and βHCG) is an independent prognostic factor.

What can be implied from the study results? First, we have identified a subgroup of patients with higher probability to achieve durable remission by conventional salvage chemotherapy. Salvage chemotherapy with conventional dose cisplatin plus previously not utilized drugs (ifosfamide, vinblastin) will cure 20-25% of patients who were not initially cured with their induction chemotherapy [5, 6, 7, 8]. In this retrospective analysis 34% patients achieved durable remission to salvage chemotherapy. However, 58% of patients with favourable marker decline achieved durable response in comparison to 7% patients with unfavourable marker decline. Traditionally, testis primary and CR to induction chemotherapy are the strongest predictors to durable response to salvage chemotherapy [2]. In our analysis these patients had not significantly better outcome. However, this could be influenced by small sample size of the study.

Recently, Massard et al. analyzed the prognostic value of serum tumor marker decline in the IT94 phase III randomized trial which compared conventional salvage chemotherapy (4 cycles of cisplatin, ifosfamide, and vinblastine [VeIP]) with high-dose chemotherapy (3 cycles of VeIP followed by 1 cycle of high-dose carboplatin, etoposide, and cyclophosphamide). In his analysis serum AFP decline was significantly associated with PFS while serum βHCG decline did not affect the outcome. Among the patients with favourable AFP decline, those who were treated in the high-dose chemotherapy arm had better PFS and a trend for better OS compared with the patients who were in the conventional chemotherapy arm. In contrast, among the patients with an unfavorable AFP decline, those who received conventional chemotherapy had better PFS and non-significant trend for better OS compared with those who received high-dose chemotherapy [12]. In our analysis we observed, that both βHCG and AFP marker decline affect PFS and OS and this was maintained in the multivariate analysis as well. However, in the comparison to IT94 trial we observed more favourable responses to salvage chemotherapy (65% vs 53%), which could be influenced by different treatment regimens used in our patients. Because, only 4% of our patients underwent high-dose chemotherapy (HDCT) we cannot assess influence of marker decline on outcome after HDCT.

Few years ago the authors from the Memorial Sloan-Kettering Cancer Center (MSKCC) reported, that the rate of serum tumor marker decline during the first two cycles of therapy was predictive of event-free and overall survival in 54 patients treated with ifosfamide-based salvage therapy [13]. However, MSKCC study uses different method of tumor marker decline measurement and the category (e.g. favourable or unfavorable marker decline) is not completely overlapping with our definition. MSKCC method requires multiple tumor marker monitoring, and type of decline (favourable or unfavourable) is known only after two or three cycles of chemotherapy. This compromise the possiblity of early treatment change in patients with unsatisfactory serum tumor marker decline.

Secondly, our results stress the importance of looking for novel treatment strategies focusing on the group of patients with unfavourable serum marker decline. It remains to investigate whether dose intensification or increasing the

dose density could be of value in these patients. However, based on the study of Massard et al, it seems that high dose therapy is not associated with better outcome in patients with unfavourable serum marker decline. [12]. In contrast, in subgroup analysis Motzer et al showed that, patients with unfavourable marker decline have more benefit from high dose chemotherapy in first line setting [14]. However, in this trial different method of evaluation of serum tumor marker decline was used. Future trials of salvage chemotherapy should consider serum tumor marker decline as an important prognostic factor to take into account in stratifying the patients after one cycle of conventional dose salvage chemotherapy according to their risk of progression and survival. Similar approach is currently used in multi-institutional international clinical trial in the first line treatment of the patients with poor prognosis GCT´s [11].

The limitation of this trial is the retrospective nature of analysis and so the study results are only hypothesis generating. Small sample size, heterogenous patient population and heterogenity of used salvage regimen and long time period might affect the study results. On the other hand, majority of the patients in our analysis were treated according daily clinical practice, which might increase generalizability of the serum tumor marker decline prognostic value. Because, no patient who progressed within the month after the end of 1st line therapy was included to analysis, the study results cannot be aplicated to this poor prognosis patient´s population. Only 8 (11%) of analyzed patients had extragonadal tumors, therefore we cannot asses the true impact of marker decline in these patients. Lactic dehydrogenase is another serum tumor marker in GCT´s. We didn´t take it into account because of insufficient data for such analysis.

Finally, despite the aforementioned limitations our results indicate that serum tumor marker decline is a strong independent prognostic factor on patient outcome after salvage chemotherapy. Prospective studies of different approaches in this patient population based on serum tumor marker decline are warranted.

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