Prognostic Significance of Marker Half-life during Chemotherapy in Non-seminomatous Germ Cell Testicular Tumors

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Decrease in serum alpha-fetoprotein (AFP) and human chorionic gonadotropin (HCG) levels is considered as a response during chemotherapy of non-seminomatous germ cell testicular tumors, but data on the prognostic significance of marker half-life remains inconclusive. Serum marker half-life was evaluated in 34 patients with elevated markers, receiving chemotherapy (CT). Marker half-life was calculated from the natural logarithm of the sequential AFP or HCG concentrations. The correlation between event-free (EFS) and overall survival (OS) with unfavorable half-lives of AFP and HCG was evaluated. Median actual half-life (AHL) AFP was 3.9 days (range, 1.4–21.5) and median AHL HCG was 4.4 days (range, 1.4–21.0); 82% of the patients had a satisfactory initial decline in AFP, and 71% had a satisfactory initial decline in HCG. There was a significant difference in EFS and OS between the two groups of patients with an AFP half-life <7 days and >7 days. HCG half-life did not adversely affect EFS and OS. The correlation of better EFS and OS with appropriate AFP marker half-life during chemotherapy could provide a dynamic method, which could complement the standard baseline prognostic factors, for the prediction of prognosis.

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The importance of the serum tumor markers alpha-fetoprotein (AFP) and human chorionic gonadotropin (HCG) in the diagnosis and treatment of non-seminomatous germ cell tumors (NSGCT) is well known. The serum tumor marker level at any one time is determined by the production of marker by the tumor and clearance from the plasma (1). The rate of decrease in serum marker levels following treatment is called the actual half-life (AHL) of the marker (2). The AHL of AFP and HCG after orchidectomy and/or lymphadenectomy is 5–7 days and 1–3 days, respectively (2). Longer AHL indicates incomplete removal of the tumor. Decrease in marker levels during chemotherapy is used for monitoring response to treatment (3–5). Effective chemotherapy (CT) is expected to decrease marker production, thus shortening marker AHL. In contrast, ineffective CT may lead to a prolongation of the marker AHL. The prognostic significance of marker AHL in NSGCT was first reported by Kohn et al. (2). This study showed the correlation between AFP AHL and the prognosis of teratoma. Later, Lange et al. developed formulae for the calculation of marker half-life (T1/2) (6). The results of the study led to the conclusion that changes in marker synthesis were the initial signs of cellular response to CT. Other studies reported contradictory results on the prognostic significance of the AFP and HCG AHL measured during CT (7, 8).

We retrospectively investigated the correlation of marker AHL during CT and disease outcome, and determined the prognostic influence of marker AHL on event-free (EFS) and overall (OS) survival.

MATERIAL AND METHODS

Patients with testicular germ cell tumors who were referred to the clinic between 1987 and 1993 were retrospectively reviewed. Thirty-four patients who received standard CT, who had elevated serum marker levels prior to CT, had recorded marker levels after the first cycle of CT, and were evaluable for survival analysis were included in the study. OS was calculated from the first day of treatment and EFS from the first day of treatment until the first event, which was defined as relapse in patients with complete response, and death in those with partial response. Marker levels were measured by microparticle enzyme immunoassay (MEIA) technology (IMx AFP and IMx total HCG as-

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says, Abbott Lab., Diagnostics Division-Chicago). Marker levels recorded before CT and before the second cycle (each cycle 21 days apart) were used for AHL analysis. AHL was determined using the method from Lange et al. (6).

$$\text{slope} = (y0 - Y)\,(t0 - T) + (y1 - Y)\,(t1 - T)$$

$$(t0 - T)2 + (t1 - T)2$$

$$Y = y0/2 + t1/2$$

$$T = t0/2 + t1/2$$

Favorable AHL was defined as $T1/2 < 3$ days for HCG, $T1/2 < 7$ days for AFP and $T1/2 < 5$ days for the combination of HCG and AFP. EFS and OS analysis of patient groups with favorable and unfavorable marker AHL was carried out using the Kaplan–Meier (KM) method, and the results were compared with the logrank test.

RESULTS

All 34 patients had elevated AFP (IU > 10 IU/ml) and 21 (62%) of them also had elevated HCG (mIU > 15 mIU/ml). Patient characteristics are presented in Table 1. Patients with stage I disease included in the study had persistent and increasing serum marker levels after orchidectomy. After receiving cisplatinum-based combination chemotherapy, 44% of the patients achieved a complete radiologic response (CR) and 56% a partial radiologic response (PR). Median AHL AFP was 3.9 days (range, 1.4–21.5) and median AHL HCG was 4.4 days (range, 1.4–21.0). Using the description above, 28 patients (82%) had a favorable initial decline in AFP, and 15 patients (71%) had a favorable initial decline in HCG (Table 2).

Table 1

Characteristics of 34 patients

Characteristics	Patients (%)
No. patients	34
Elevated serum tumor markers before chemotherapy	
No. elevated AFP (IU >10 IU/ml)	34 (100%)
Median 178	
Range 25–15 520	
No. elevated HCG (mIU<15 mIU/ml)	21 (62%)
Median 23.5	
Range 0–4 000	
No. elevated AFP and HCG	21 (62%)
Primary site	
Testis	34 (100%)
Histology	
Combined	14 (42%)
Teratoma	9 (26%)
Embryonal carcinoma	9 (26%)
Endodermal sinus tumor	1 (3%)
Mixed with seminoma	1 (3%)
Stage	
I	9 (26%)
II	18 (53%)
III	1 (3%)
IV	6 (18%)
Type of cisplatinum-based combination CT	
PEB	19 (56%)
Intensive combination CT (POMB/ACE, VIP)	15 (44%)
Current status	
Alive with no evidence of disease	26 (77%)
Alive with progression	2 (6%)
Dead with disease progression	6 (17%)

AFP = alphafetoprotein; HCG = human chorionic gonadotropin.

Table 2

Treatment characteristics

Radiologic response	
Complete	44%
Partial	56%
AHL AFP	
Median	3.9 days
Range	1.4–21.0 days
AHL HCG	
Median	4.4 days
Range	1.4–21.0 days
Favorable AHL AFP	28 (82%)
Favorable AHL HCG	15 (71%)

A favorable decline in AFP strongly correlated with improved survival (KM, logrank $p = 0.0006$ for EFS and $p = 0.03$ for OS). The median EFS and OS for the group with unfavorable AHL AFP was 20 and 24 months, respectively, whereas the median survival for patients with an appropriate AHL AFP has not been reached yet (Figs. 1 and 2).

Favorable AHL HCG did not have a significant influence on either OS (Table 3, $p = 0.73$), or EFS (Table 3, $p = 0.46$).

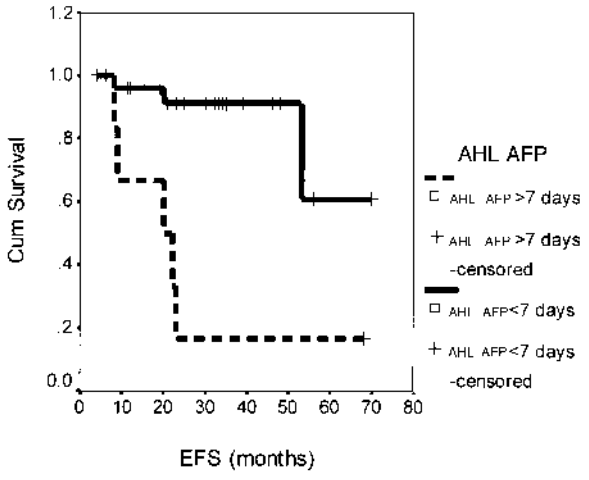

Fig. 1. Event free survival in non-seminomatous germ cell testicular tumors (NSGCTT) patients with favorable and unfavorable AHL AFP (Kaplan–Meier, logrank $p = 0.0006$).

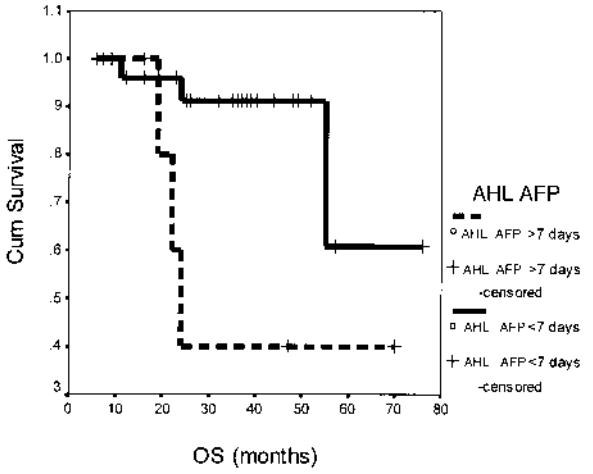

Fig. 2. Overall survival in NSGCTT patients with favorable and unfavorable AHL AFP (Kaplan–Meier, logrank p = 0.03).

There was no difference in survival between patients (19 pts.) who received the standard BEP regimen and those (15 pts.) treated with more intensive CT. When the survival analyses comparing the chemotherapy regimens were adjusted for favorable and unfavorable AHL AFP, there were still no significant differences in either overall or event-free survival (p = 0.42 and p = 0.56, respectively) (Table 4).

DISCUSSION

Alpha-fetoprotein and/or beta human chorionic gonadotropin levels are elevated in 80% to 90% of patients with NSGCT at the time of diagnosis (9). They have the highest specificity and sensitivity among the known serum tumor markers in the diagnosis and treatment of cancer. The pharmacokinetics of AFP and HCG have been investigated in detail, in the hope of finding a guide toward making decisions on the treatment of patients with germ cell tumors.

The mortality rate for non-seminomatous germ cell testicular cancer has declined dramatically in the past two decades following the introduction of cisplatinum-based combination chemotherapy. At present, serum levels of AFP and HCG are used in the definition of risk groups in patients with NSGCT (10). Marker kinetics evaluated by measurements during each cycle of CT rather than static initial measurements may better reflect the prognosis of NSGCT. Favorable initial decline in marker rates would correspond to cessation of all in vivo marker production, and therefore, to the efficacy of CT. On the other hand, an AHL AFP greater than 7 days and AHL HCG greater than 3 days after the first cycle of chemotherapy may represent inappropriate decline and indicate patients who are likely to fail initial CT. The prognostic significance of marker decline may be an aid in defining high-risk patients who will be candidates for more intensive salvage CT, or high-dose chemotherapy with stem cell rescue as late intensification (11).

Previous studies are inconclusive in terms of the exact definitions for the prognostic value of unfavorable marker decline. Horwich et al. have reported transient tumor marker evaluation following CT for germ cell cancer, the so-called 'surge effect' (12). This surge effect could only be determined by frequent, i.e. weekly, marker measurements, and it was not an adverse prognostic factor. Lange et al. have suggested that AFP and HCG synthesis is among the first cellular activities to respond to chemotherapy (13). They have studied the relationship of response with AHL AFP and AHL HCG, and found that marker half-life was independent of initial tumor bulk, and favorable AHL was closely correlated with better response to treatment. The study concluded that a favorable actual half-life had prognostic value only if the treatment could be completed and was not a guarantee against relapse. Horwich & Peckham studied 67 patients with NSGCT during chemotherapy and concluded that, with the well-known effective CT regimens, a fall in tumor marker levels rarely had prognostic significance (7). Murphy et al. investigated the role of serum tumor marker regression as a post-treatment prognostic indicator for response, EFS, and OS in 54 patients with NSGCT (8). In this study, the rate of serum tumor

Table 3

Survival by favorable (F) or unfavorable (UF) marker decline

Marker decline*	No	No. event-free	Median EFS	p	No. alive	Median OS	p
UF AHL HCG	12	9 (75%)	55	0.46	10 (83%)	55	0.73
F AHL HCG	9	1 (89%)	NR		1 (89%)	NR	
UF AHL AFP	6	1 (17%)	20	0.0006	3 (50%)	24	0.03
F AHL AFP	28	25 (89%)	NR		25 (89%)	NR	
UF AHL AFP-HCG	12	9 (75%)	53	0.46	2 (83%)	55	0.73
F AHL AFP-HCG	9	1 (89%)	NR		1 (89%)	NR	

UF = unfavorable; F = favorable; AFP = alphafetoprotein; HCG = human chorionic gonadotropin; NR = :not reached; AHL = actual half-life; EFS = event-free survival, months; OS = overall survival, months.
* Favorable and unfavorable marker decline for AFP and HCG is explained in the Material and Methods section of the text.

Table 4

Survival in favorable (F) and unfavorable (UF) AHL AFP adjusted by CT regimens

Type of chemotherapy	No. patients	No. event-free	Median EFS*	p	No. alive	Median OS*	p
Favorable AHL AFP							
PEB	17	16 (94%)	53	0.56	16 (94%)	55	0.42
Other	11	9 (82%)	NR		9 (82%)	NR	
Unfavorable AHL AFP							
PEB	2	0	9		1 (50%)	19	
Other	4	1 (25%)	20		2 (50%)	24	

AFP = alphafetoprotein; HCG = human chorionic gonadotropin; NR = not reached; AHL = actual half-life.
* Survival in months.

marker decline, particularly for HCG, was found to be a useful tool in predicting treatment outcome, and for directing a treatment change to more intensive therapy. Stevens et al. investigated initial marker decline in 184 patients with NSGCT receiving cisplatinum-based CT, in order to determine whether initial marker decline was an important prognostic factor (14). This study identified a prolonged marker half-life to be an indicator of higher mortality risk, but the positive predictive value was low. A more recent analysis of 669 patients by de Wit has revealed no significance of marker half-life, but significant prognostic value for initial tumor marker concentrations (15). Our study, although encompassing a rather small number of patients, has shown that AHL AFP strongly predicts better survival. The timing of marker measurements was chosen to avoid the 'surge effect'. The low number of patients with HCG elevation and the modest degree of HCG elevation (maximum level 4 000 IU/ml) may have led to the lack of survival advantage with satisfactory AHL HCG. If confirmed in a larger series of patients, the finding of unsatisfactory marker decline may become a useful guide in defining poor-risk patients who will be candidates for dose-intensification trials. The results of the study include an analysis comparing survival independent of marker decline between patients receiving BEP and other initial intensive regimens. The lack of evidence for better survival with more intensive initial CT instead of the 'gold standard' BEP regimen has recently been verified in a randomized trial (16).

In conclusion, the prognostic significance of marker kinetics during CT remains to be determined. Present studies vary greatly in the frequency of serial marker measurements, the methods used for the calculation of decline, and the comparison of marker kinetics with response or survival. A large study using frequent standardized marker follow-up during CT and comparing marker kinetics with event-free and overall survival may be conclusive in defining the true role of marker kinetics in the treatment of NSGCT.

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