Does Serum Tumor Marker Half-Life Complement Pretreatment Risk Stratification in Metastatic Nonseminomatosus Germ Cell Tumors?

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ABSTRACT
The goal of this study was to determine whether the serum tumor marker half-life (MHL) of human chorionic gonadotropin (HCG) and α-fetoprotein (AFP) during initial chemotherapy can complement pretreatment risk stratification in metastatic nonseminomatous germ cell tumors. One hundred forty-seven patients were assessable for MHL during the first two cycles of platinum-based chemotherapy. MHL calculation was based on two consecutive values using Kohn’s apparent half-life formula (MHL = ln10G, where G was the gradient of the marker slope) or on three (or more) values using simple linear regression. MHL was regarded as prolonged if it was more than 3.5 days for HCG or more than 7 days for AFP. The median MHL for HCG was 2.8 days (range, 0.7–16.7) and for AFP was 6.2 days (range, 2.6–65.4). Thirty-five of 108 patients (32%) had a prolonged MHL for HCG, 41 of 114 (36%) had a prolonged MHL for AFP, and in 59 of 147 patients (40%), either or both MHLs were prolonged. If patients with both MHLs normal were compared against patients with either or both MHLs prolonged, highly significant differences in progression-free survival (P < 0.0001) and overall survival (P = 0.0005) were demonstrated. The test accuracy was 70% for both progression-free and overall survival, and it was slightly greater than the overall predictive value of the Medical Research Council prognostic classification. A combination of Medical Research Council criteria and MHL analysis allowed us to refine prognostic assessment. Because MHL analysis is able to complement pretreatment risk stratification and can support selection of patients for early-dose intensified chemotherapy, it should be included in prospective clinical trials for patients with poor-prognosis disease.

INTRODUCTION
Despite the advances of cisplatin-based chemotherapy, approximately 15–20% of patients with metastatic NSGCTs ultimately die of their disease (1, 2). Age, primary mediastinal versus testicular/retroperitoneal origin, number of metastatic sites, number and size of metastatic lesions, specific sites of disease (liver, brain, or bone metastases), and the levels of lactate dehydrogenase and tumor markers HCG and AFP can be used to divide patients into good- and poor-prognostic categories (1–3). In a recent multivariate analysis including 795 patients with metastatic NSGCTs, a good-prognosis group comprised two-thirds of the population and had a 5-year survival rate of 92%, whereas only 60% of the remaining poor-prognosis patients were alive at 5 years (2).

Because a considerable proportion of poor-prognosis patients is not cured by standard treatment, more aggressive approaches including high-dose chemotherapy with autologous stem cell support have been investigated. If, however, all poor-prognosis patients were given high-dose chemotherapy as part of their primary treatment, approximately 60% would receive a toxic and costly overtreatment. On the other hand, after failure of front-line chemotherapy, only 20–30% of patients can be cured by conventional salvage chemotherapy (4–6). Although high-dose chemotherapy may improve the outcome of patients at first relapse, it still fails to cure a considerable proportion of patients (7). Early treatment intensification before overt relapse is therefore a reasonable concept. For this purpose, appropriate posttreatment prognostic variables are needed to recognize suboptimal response at an early stage.

Whereas the eminent role of serum tumor markers HCG and AFP in pretreatment risk stratification is generally accepted today (8), the prognostic value of early MHL during primary chemotherapy is controversial (9–11). We therefore reviewed our single-institution experience with particular reference to whether MHL analysis can complement pretreatment risk stratification.

PATIENTS AND METHODS
Two hundred sixty-three men with metastatic NSGCTs underwent first-line platinum-based chemotherapy at Klinikum Grosshadern between May 1979 and April 1995. A total of 215 patients (82%) had elevated serum tumor markers HCG and/or

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2 The abbreviations used are: NSGCT, nonseminomatous germ cell tumor; HCG, human chorionic gonadotropin; AFP, α-fetoprotein; MHL, marker half-life; MRC, Medical Research Council; CR, complete response; PR, partial response; PD, progressive disease; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval.
AFP at the start of chemotherapy. Marker measurements were performed as described elsewhere (12, 13). All values for HCG >5 IU/liter and for AFP >15 IU/ml were regarded as elevated. One hundred forty-seven patients had at least two abnormal markers more than 7 days after commencement of chemotherapy, which allowed the determination of MHL. Some patients were included in a previous report (11).

Staging consisted of history and physical examination, chest X-ray, abdominal and thoracic computerized tomography, and serum tumor markers HCG and AFP. Patients were divided into two prognostic groups as defined by MRC criteria (2). One hundred one patients (69%) with liver, bone, or brain metastases; a mediastinal mass >5 cm; 20 or more lung metastases; HCG >10,000 IU/liter; and/or AFP >1000 IU/ml constituted a poor-prognosis group. Forty-six patients (31%) without any of these features were considered as good-prognosis patients. The proportion of poor-prognosis patients was 47% in the total group of 263 patients and was selected by tertiary referral. The exclusion of patients with normal and slightly elevated markers who did not qualify for MHL analysis led to further selection of poor-prognosis patients. Median age at diagnosis was 27 years (range, 16–55). One hundred twenty-one patients had tumors of testicular origin, whereas 26 tumors arose at extragonadal sites (10 in the mediastinum, 16 in the retroperitoneum). Twenty-five of 26 extragonadal tumors were assigned a poor prognosis according to MRC criteria.

Until 1984, all patients received chemotherapy according to the “PVB” schedule consisting of 20 mg/m² cisplatin on days 1–5, 0.15–0.20 mg/kg vinblastine on days 1 and 2, and 30 mg bleomycin on days 2, 9, and 16 (1). Since 1984, patients with a large tumor burden have been treated predominantly according to the “ECBC” schedule consisting of 120 mg/m² etoposide on days 1–4, 30 mg/m² cisplatin on days 1–4, 15 mg bleomycin on day 1 (bolus), 12 mg/m² bleomycin on days 1–4 (24-h infusion), and 300 mg/m² cyclophosphamide on days 1–4 (14). In 1987, we began to treat patients with low-volume metastatic disease according to the “BEP” regimen, substituting etoposide 100 mg/m² on days 1–5 for vinblastine (15).

CR was defined as disappearance of all clinical, radiological, and serological evidence of disease. Patients who underwent complete postchemotherapy resection of residual masses containing viable carcinoma were coded as CR + SURG. Patients who achieved normalization of tumor markers but had unresectable tumor residuals were classified as PR. PD was defined as progression before discontinuation of scheduled treatment or within 1 month after the last chemotherapy cycle. The median follow-up duration from the date of initiation of chemotherapy was 88 months (range, 6–186).

Marker values were plotted semilogarithmically (in concentration versus linear time); MHL calculation was based on two consecutive values using Kohn’s apparent half-life formula (MHL = ln2/G, where G was the gradient of the marker slope; Ref. 16) or on three (or more) values using simple linear regression, if the regression coefficient was not lower than 0.90. Regression analysis was the preferred method of MHL determination, because it is less affected by test variability than is Kohn’s apparent half-life formula. If only two abnormal marker values more than 7 days after start of chemotherapy were available, Kohn’s half-life formula was used for calculation; an interval of at least 7 days between the two measurements was required. The first values measured more than 7 days after the beginning of chemotherapy were used for calculations, because the peak of marker surge was observed mainly within the first week (17). There were three exceptions; in two cases, the peak of marker surge occurred on day 8 for HCG, and in one case on day 9 for AFP. Only marker values measured during the first two cycles of chemotherapy were considered for MHL. In contrast to two recent reports (9, 10), the cutoff of MHL was chosen at 3.5 days for HCG, as patients with MHLs between 3.1 and 3.5 days had a prognosis similar to those of patients with shorter MHLs. Of 60 patients with MHL for HCG ≤3.0 days, 35% developed PD and 30% died; of 13 patients with a MHL between 3.1 and 3.5 days, 31% developed progression and 23% died. In concordance with the other reports, a MHL of ≤7 days was defined as normal for AFP. As in the report by Toner et al. (9), marker regression was considered normal if both MHLs were within the above-mentioned limits or if one was within these limits and the other was not assessable.

Patients with normal and prolonged MHLs were compared for each marker against the end points of response, PFS and OS. Differences in proportions were tested using χ² and Fisher’s exact tests. MHLs of subgroups of patients were compared using the Mann-Whitney U test. Survival distributions were estimated by the Kaplan-Meier method from the date of initiation of chemotherapy (18). Comparative survival of patients was measured using the log-rank test (19). P values <0.05 were regarded as statistically significant.

RESULTS

In 58 cases (54%), HCG MHL was determined by regression and in 50 cases (46%), by the half-life formula of Kohn (16). Similarly, AFP MHL was determined by regression in 63 cases (55%) and by Kohn’s (16) half-life formula in 51 cases (45%). Nineteen of 58 HCG MHLs (33%) determined by regression were prolonged compared to 16 of 50 (32%) measured by Kohn’s (16) formula; similarly, 21 of 63 AFP MHLs (33%) determined by regression were abnormal compared to 20 of 51 (39%) measured by Kohn’s (16) formula (P values >0.05, χ² test). Median MHLs for HCG (AFP) were 2.8 (5.7) and 3.0 (6.4) days for regression and Kohn’s (16) formula, respectively. The distributions of MHLs did not differ in the subgroups defined by the method of MHL analysis (P values >0.05, Mann-Whitney U test).

The median times to first and last marker values used for half-life calculation were 9 days and 25 days (HCG) or 32 days (AFP), respectively. Of the patients with HCG values after day 25, 23 of 53 (43%) had prolonged MHLs compared to 12 of 55 patients (22%), with values up to day 25 (P < 0.03, χ² test). The medians of MHLs in both subgroups were 3.4 and 2.6 days, respectively; the distributions of MHLs in both subgroups were significantly different (P < 0.002, Mann-Whitney U test). In the group with AFP values after day 32, 24 of 55 patients (44%) had prolonged MHLs compared to 17 of 59 patients (29%) with values up to day 32 (P = 0.09, χ² test). The medians of MHLs in both subgroups were 6.3 and 5.9 days, respectively; the distributions of MHLs in both subgroups were significantly different (P < 0.05, Mann-Whitney U test).
Table 1  Value of MRC criteria (2) as a test of prognosis

<table>
<thead>
<tr>
<th>Test</th>
<th>Positive predictive value (%)</th>
<th>Negative predictive value (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Test accuracy (%)</th>
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<tbody>
<tr>
<td>PFS</td>
<td>59</td>
<td>79</td>
<td>86</td>
<td>47</td>
<td>65</td>
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<tr>
<td>OS</td>
<td>52</td>
<td>80</td>
<td>85</td>
<td>43</td>
<td>61</td>
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</table>

Considering the group as a whole, the median MHL for HCG was 2.8 days (range, 0.7–16.7) and for AFP was 6.2 days (range, 2.6–65.4). Thirty-five of 108 patients (32%) had a prolonged MHL for HCG, 41 of 114 (36%) had a prolonged MHL for AFP, and in 59 of 147 patients (40%), either or both MHLs were prolonged. Of the 75 patients assessable for both MHLs, a high concordance rate of 76% was shown (i.e., either both normal or prolonged). No relationship was found between tumor volume and MHL. Either or both MHLs were prolonged in 20 of 46 good-prognosis patients (43%) and in 39 of 101 poor-prognosis patients (39%) according to MRC criteria, respectively ($P = 0.7$, $\chi^2$ test). However, the type of chemotherapy had an impact on MHL. Twenty-five of 45 poor-prognosis patients (56%) receiving vinblastine-containing chemotherapy had an abnormal MHL, whereas only 14 of 56 poor-prognosis patients (25%) receiving etoposide-containing protocols had a prolonged MHL ($P < 0.01$, $\chi^2$ test).

Six patients were not assessable for response because of early death within 2 months from the start of chemotherapy; in four of these cases, either MHL was normal and in two, prolonged. For the remaining 141 patients, the relationship between MHL and the category of response is depicted in Fig. 1. Sixty-eight of 101 patients (67%) who achieved a CR or CR + SURG had normal values for both MHLs, whereas only 16 of 40 patients (40%) with an incomplete response (PR or PD) had normal MHLs ($P < 0.01$, $\chi^2$ test).

Five-year OS was 88% in the good-prognosis group and 56% in the MRC poor-prognosis group. Comparing MRC prognostic groups, the HRs for PFS and OS were 2.7 (95% CI, 1.5–5.0) and 3.1 (95% CI, 1.6–7.7), respectively. Sensitivity, specificity, and test accuracy of the MRC prognostic classification are listed in Table 1.

The impact of MHL on PFS and OS is depicted in Figs. 2–5. Ten-year survival rates and HRs are listed in Table 2. Patients with prolonged MHLs for HCG had an inferior PFS ($P = 0.001$) and OS ($P = 0.003$) compared with patients with normal MHLs. Similarly, significant differences in PFS ($P = 0.01$) and OS ($P = 0.02$) were found for patients with abnormal MHLs for AFP compared with patients with normal MHLs. If patients with both MHLs normal were compared against patients with either or both MHLs prolonged, highly significant differences in PFS ($P < 0.0001$) and OS ($P = 0.0005$) were demonstrated. The test accuracy was 70% for both PFS and OS (Table 3).

MHL also had an influence on the incidence of late relapse. Of 56 patients with normal MHLs who remained at risk of progression 2 years after discontinuation of primary treatment, only one (1.8%) developed a late relapse. In contrast, 9 of 30 patients (30%) with one or both MHLs abnormal developed a late relapse ($P < 0.0001$, Fisher’s exact test).
DISCUSSION

Because the correct overall prediction of pretreatment staging systems for advanced NSGCTs is only around 60–80% (20, 21), appropriate posttreatment prognostic variables are needed to detect treatment failure at an early stage. Early reports suggested that MHL during initial chemotherapy may be a useful predictor of clinical outcome (22, 23). A few years ago, investigators from Memorial Sloan-Kettering Cancer Center described their 10-year experience with MHL analysis in 198 men treated since 1979 (9). The authors found that MHL correlated significantly with response and survival, and MHL analysis provided prognostic information in addition to pretreatment risk assignment. MHL was determined in only one-third of patients; the median time to first and second marker assays was 30 days and 56 days (AFP) or 59 days (HCG), respectively. The remaining patients with either of the first two marker values (measured 7–90 days after initiation of chemotherapy) being normal were included in the group with satisfactory marker decline. This study thus combined MHL analysis with early marker remission, which is itself a predictor of good prognosis. Patients with prolonged MHL had a relative risk of death of 3.63 compared to patients with either normal MHL or early marker remission (9).

Two recent reports included only patients with calculable MHLs (10, 11). In our own early experience, we could not find a significant influence of MHL on OS in a group of poor-prognosis patients as defined by the Indiana University staging system (11). However, this study included a relatively small number of patients, and it did not examine combinations of HCG and AFP MHLs. A report from Royal Marsden Hospital (10) included 183 patients who had MHL determinations between days 7 and 22 after commencement of chemotherapy. This report described a correlation between MHL and response and OS, which was only significant if markers were examined in combination. However, no significant correlation was found between MHL and PFS; the test accuracy was only 57%. The authors concluded that early evaluation of MHL was not able to predict patients at higher risk of progression after front-line chemotherapy and that it was a poor guide to long-term prognosis.

A major reason for the discordance of previous publications probably is the different methodology used to measure MHL. The half-life determination of Kohn (16), using only two values, is more affected by test variability than regression analysis and is therefore less reliable in an individual patient. Consequently, the formula of Kohn (16) was used if only two abnormal values after day 7 were available or if marker values scattered too much and the correlation coefficient was lower than 0.9. We could not find a significant correlation between the method of MHL determination and the proportions of patients with normal and prolonged MHLs. Of greater importance appears to be the timing of measurement. Although MHL analysis was restricted to the first two cycles of chemotherapy in our study, we found that the proportion of patients with prolonged MHLs increased with later measurements.
demonstrated that patients with poor-prognosis disease and prolonged MHL during the first two cycles of conventional chemotherapy and were therefore selected for two cycles (25).

Cancer Center published the results from a Phase II trial including 28 patients with poor-prognosis disease as defined by pretreatment stratification (9). MHL analysis should be restricted MHL analysis to the first two cycles of chemotherapy to identify additional patients at an increased risk of treatment failure. However, for clinical practice, it may be reasonable to restrict MHL analysis to the first two cycles of chemotherapy to get an early reassessment of prognosis in an individual patient. Apart from the methodology used for calculation, the type of chemotherapy (etoposide-containing versus vinblastine-containing) was found to have an impact on MHL in poor-prognosis patients. In a multivariate analysis, we recently identified etoposide-containing chemotherapy as an independent predictor of favorable outcome in poor-prognosis disease (24). This finding compares favorably with a Phase III trial by Williams et al. (15) who described a superiority of etoposide compared with vinblastine in a subgroup of poor-prognosis patients. However, cumulative experience and advances in supportive care that allowed the administration of a higher dose intensity may also explain the decreasing proportion of patients with prolonged MHLs during more recent years.

Recently, investigators from Memorial Sloan-Kettering Cancer Center published the results from a Phase II trial including 28 patients with poor-prognosis disease as defined by pretreatment stratification (25). Twenty-two of these 28 patients had a prolonged MHL during the first two cycles of conventional chemotherapy and were therefore selected for two cycles of high-dose carboplatin and etoposide. Given that our study demonstrated that patients with poor-prognosis disease and prolonged MHL have a low chance of long-term disease-free survival, such an aggressive approach seems justified. Whether such an approach is superior to conventional dose chemotherapy can only be evaluated in a randomized trial.

In conclusion, MHL analysis during the first two cycles of platinum-based chemotherapy provides prognostic information in addition to pretreatment risk stratification. The overall predictive value of MHL is slightly greater than for pretreatment risk assignment by MRC criteria. MHL analysis should be included in prospective clinical trials for patients with poor-prognosis disease.

### REFERENCES


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