Stage Migration and the Increasing Proportion of Complete Responders in Patients with Advanced Germ Cell Tumors

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ABSTRACT

The proportion of patients with metastatic germ cell tumors achieving complete remission increased, and the total survival improved between 1975 and 1982. Several analyses were undertaken to evaluate the influence of stage migration on treatment outcome in patients with germ cell tumors. (a) A logistic regression analysis showed that a formulation of time was an independent statistically significant variable ($P = 0.025$) in addition to the total number of sites of metastasis ($P < 0.001$) and pretreatment values of human chorionic gonadotropin ($P < 0.001$) and lactate dehydrogenase ($P = 0.002$). (b) The proportion of patients with lung metastases and elevated levels of human chorionic gonadotropin and $\alpha$-fetoprotein decreased, and the number of patients with retroperitoneal metastases and without prior radiation therapy increased significantly. (c) The number of patients with a high likelihood of complete response increased significantly over time ($P < 0.001$). Computerized tomography of the abdomen permits detection of large but asymptomatic retroperitoneal disease, and such patients are now being treated with chemotherapy rather than surgery and are included in advanced disease treatment results. Stage migration has played a role in the increasing proportion of complete responders in clinical trials of patients with germ cell tumors.

INTRODUCTION

The addition of cisplatin in the mid-1970s to combination chemotherapy programs led to strikingly improved survival of patients with metastatic GCT. Although cure rates greater than 90% have been reported (1), methods of both treatment and disease detection have improved. Short, intensive induction is now the accepted mode of therapy, and CT is now routinely used as a staging procedure. CT scans of the abdomen can detect asymptomatic retroperitoneal disease which previously would have gone undetected.

"Stage migration" has been defined as the movement of a cohort of patients from a less to a more advanced disease category, resulting in misleading survival statistics. At least two factors may contribute to this reclassification of patients. (a) It may result from improved detection of metastases. Feinstein et al. (2) recently showed that improvement in the survival of patients with lung cancer of Stages II and III occurred between 1953 and 1977 as a result of improved detection of occult metastatic disease. (b) The proportion of patients achieving CR increased significantly over time ($P < 0.001$). Computerized tomography of the abdomen permits detection of large but asymptomatic retroperitoneal disease, and such patients are now being treated with chemotherapy rather than surgery and are included in advanced disease treatment results. Stage migration has played a role in the increasing proportion of complete responders in clinical trials of patients with germ cell tumors.

Between 1975 and 1982, patients with metastatic GCT of the testis were treated with successive chemotherapy programs which included high doses of cisplatin (120 mg/m$^2$/cycle). The drugs, doses, and schedules of VAB-3, VAB-4, VAB-5, and VAB-6 have been previously reported (5–8). The proportion of patients achieving CR increased during this time from 54% to 79%.

In order to evaluate important clinical changes with time, several variables were measured. Pretreatment values of AFP, HCG, and LDH were routinely obtained. The location of organ-specific metastases and the number of metastatic sites were recorded.

We have reported a logistic regression analysis of prognostic variables in patients with testicular GCT (9). The statistically significant prognostic variables for CR were the number of sites of metastasis and logarithmic transformations of the actual pretreatment values of LDH and HCG. Neither AFP, assessment of tumor size per se, nor treatment protocol achieved statistical significance as independent prognostic factors. The resulting mathematical model was used to calculate the
probability of CR for each patient based upon an individual's pretreatment clinical characteristics.

For the purposes of this study, patients achieved either a CR or an IR. A CR required the complete disappearance of all clinical, radiographical and biochemical evidence of disease after chemotherapy alone or the complete absence of evidence of disease following chemotherapy and resection of all residual sites of disease. Any patient not achieving a CR had an IR.

To determine whether changes in the pretreatment clinical characteristics and response to therapy were time dependent, as opposed to treatment dependent, several statistical analyses were undertaken. (a) For exploratory purposes, the medians and 95% confidence intervals for the medians for the yearly pretreatment serum tumor marker values were determined (10). (b) A x^2 test for linear trend (11) was calculated for the 2-yr intervals of 1975-1976, 1977-1978, 1979-1980 and 1981-1982. Two-yr intervals were chosen in order to avoid sparse cells in the statistical calculations. (c) In order to investigate the possibility that time was an independent prognostic variable for CR (separate from treatment), logistic regression models (12) were developed which examined not only the known prognostic clinical variables (such as marker values) and treatment protocol, but also several formulations of time.

Let Pi be the probability that Patient i with metastatic GCT achieves a CR. The logistic model assumes that

\[ P_i = \frac{\exp(H_i)}{1 + \exp(H_i)} \] (A)

where \( H_i \) is a linear function of several baseline characteristics of Patient i. The coefficients of the linear function \( H_i \) are assumed to be unknown and are estimated from available data by using the stepwise logistic regression program BMDF-2L (13). This method is identical to our past multivariate analysis of prognostic variables (9). In our 1983 model, \( H_i \) took the following form

\[ H_i = 8.514 - 1.973 \log(LDH + 1) - 0.53 \log(HCG + 1) - 1.111 \text{TOTMET} \]

where the actual pretreatment values of HCG and LDH (in ng/ml and units/liter, respectively) were substituted, and TOTMET equaled 0, 1, or 2, depending upon whether the patient had zero, one, or two or more sites of metastasis. The value (+1) was needed to avoid \( \log(0) \) for which there is no value.

As noted, the analysis herein evaluates whether or not time was a prognostic variable for CR in addition to the serum tumor markers (AFP, LDH, and HCG), the number of metastatic sites, individual sites of metastasis, and treatment regimen. Only patients with testicular GCT were included; patients with primary extragonadal GCT and those previously receiving high doses of cisplatin were excluded. A total of 271 patients were studied here (all of those with complete data for the variables considered), whereas only 171 patients had been included in the previous analysis (10). Thus, not only is the effect of time evaluated, but the conclusions of our earlier multivariate analysis are reconsidered with a larger number of patients.

To obtain an appropriate expression for a time variable, four choices were considered: (a) an increasing ordering of time by 1-yr intervals (TIME1); (b) an increasing ordering of time by 2-yr intervals (TIME2); (c) three indicator variables for protocol and time: VAB-3 (1975-1976), VAB-4, or VAB-5 (1976-1978); early VAB-6 (1979-1980); and late VAB-6 (1981-1982) (TIME3); and (d) an increasing ordering of time by protocol: VAB-3 (1975-1976); VAB-4 or VAB-5 (1977-1978); and VAB-6 (1979-1982) (TIME4).

It must be stressed that separate indicator variables for each protocol were also considered, but these were a function of treatment protocol only and not of time. In the logistic regression model, if none of the time variables was statistically significant at the 0.05 significance level, especially in the presence of other prognostic factors, this would be interpreted to mean that the probability of CR did not change with time (as we expressed time here).

Transformations of serum AFP, HCG, and LDH values were considered in addition to the actual values. As in our previous study (9), logarithmic transformations of HCG and LDH were found to be the most significant. The actual marker value and transformations of AFP never entered the models with \( P < 0.05 \). Therefore, the final logistic analysis considered the logarithmic transformations of HCG and LDH, the number of metastatic sites, and the four time variables.

In the statistical analyses, \( P \) values of 0.05 or less were regarded as significant. All \( P \) values between 0.05 and 0.10 are reported.

RESULTS

Evaluation of Trend. An unmistakable decline in the median values of HCG and AFP occurred between 1975 and 1982 (Table 1). A median value of zero was observed earlier for AFP than for HCG. An increase was also seen in the median probability of CR, as determined by the mathematical model (9).

An analysis for trend (11) was performed on several pretreatment clinical features as well as on treatment outcome (Table 2). Statistically significant decreases in the frequency of AFP and HCG elevations, the number of patients with lung metastases, and the number of patients with prior RT were identified. The decrease in prior RT occurred in both nonseminomatous GCT and seminoma. For nonseminomatous GCT, 154 of 189 (81%) treated between 1975 and 1979 and 91 of 95 (96%) treated between 1980 and 1982 received RT before referral. For seminoma, 1 of 4 (25%) and 11 of 17 (65%) treated in the same two intervals received no RT before referral. Statistically significant increases were identified in the number of patients with retroperitoneal metastases, the probability of CR, and the actual number of patients achieving CR. Trends toward a decrease in the LDH values and the number of metastatic sites were also observed.

Logistic Regression Analysis. To pursue further the impact of the year of referral on treatment outcome, time variables were included in a multivariate logistic regression (see "Patients and Methods"). Only TIME4 entered the model with \( P < 0.05 \). No pairwise interaction terms were found to improve the model. The logistic model with time is given by Equation A (see "Patients and Methods"), where

\[ H_i = 6.0690 - 1.1420 (\text{TOTMET}) - 0.3301 \log(HCG + 1) - 1.4911 \log(LDH + 1) + 0.4375 (\text{TIME4}) \] (B)

As before, TOTMET takes the value of 0, 1, or 2, depending upon whether there are zero, one, or two or more metastatic sites, and the HCG and LDH variables are the actual pretreatment marker values in ng/ml and units/liter, respectively. The term TIME4 takes the value one if the treatment protocol was VAB-3, two if VAB-4 or VAB-5, and three if VAB-6. The negative coefficients imply that the probability of CR decreases as the corresponding variable increases. For example, the probability of CR decreases as HCG increases. The positive coefficient of TIME4 implies that the probability of CR increases as time progressed from 1975-1982.

The variables in Equation B appear in the order of their explanatory power. Thus, TOTMET, which contributes the most to the model, is listed first (Table 3). Since the time variable TIME4 was statistically significant, we inferred the presence of stage migration. However, time was considerably less significant than the other three factors. The model without TIME4 (not shown) had similar coefficients, reinforcing the fact that time was the least important of the predictor variables. These results also confirm the significance of LDH, HCG, and TOTMET as prognostic factors for CR, as previously published.

Impact on Predicted and Actual Response. The predicted and
considered (probability of CR > 0.8), then 10 of 54 (19%) of patients receiving VAB-3, 39 of 83 (47%) receiving VAB-4 or VAB-5, and 77 of 134 (58%) receiving VAB-6 had an extremely high likelihood of achieving CR ($\chi^2 = 23.48$, 2 d.f., $P < 0.001$). These data suggest that the differences in treatment outcome are influenced not only by changes in treatment, but also by the referral patterns and evolving management philosophies.

**DISCUSSION**

These data show that factors other than changes in treatment have contributed to the appearance of improved cure rates in patients with GCT since the introduction of high dose cisplatin in the mid-1970s. There is no question that cisplatin at doses $\geq 100$ mg/m² and properly timed resection of residual disease are necessary to achieve CR (14). However, it is equally clear that patients with GCT treated in 1982 had a higher likelihood of achieving CR than they did in 1975. Since a time variable was a statistically significant predictor variable for CR in addition to previously established prognostic factors, the logistic model given in Equation B provides evidence for stage migration. This model says that between 1975 and 1982, the probability of CR increased with time, independent of other prognostic factors. The time variable was significant only at the $P = 0.025$ level, whereas the other prognostic factors were significant at levels $\leq 0.002$, implying that time was the least important of the prognostic factors in the model. Since the model in Equation B identified the same factors as our previously published model (9), the prognostic importance of LDH, HCG, and the total number of sites of disease is confirmed with an additional 100 patients.

Two changes in clinical practice occurred between 1975 and 1982 which probably contribute to the observed trends. (a) An increasing number of patients with "bulky" clinical Stage II disease were treated with chemotherapy. The increase in the frequency of retroperitoneal lymph node metastases and decrease in that of lung metastases support this conclusion. The routine use of CT scans of the abdomen (introduced in the late 1970s) identifies some patients with extensive but asymptomatic retroperitoneal disease which would have been undetected prior to the era of CT scanning. At Memorial Sloan-Kettering Cancer Center, the first high-quality CT scanner was installed in 1979. In the past, a RPLND initially would have been performed on such patients, and they would be treated with chemotherapy either in an adjuvant fashion or at recurrence. These data suggest that the differences in treatment outcome are influenced not only by changes in treatment, but also by the referral patterns and evolving management philosophies.

(b) RT is being used less frequently in both seminoma and nonseminomatous GCT. With the success of cisplatin-based chemotherapy, RT has assumed a palliative role in patients with advanced nonseminomatous GCT. RT still has curative potential in seminoma, but patients who relapse after RT are more difficult to manage. Full doses of chemotherapy may be impossible to administer due to severe myelosuppression, and...
the survival of those receiving extensive RT prior to chemotherapy is worse than that of those without RT (15, 16). In our recent review of patients treated for advanced seminoma, 11 of 20 (55%) referred between 1979 and 1982 and 32 of 40 (80%) referred between 1983 and 1986 had received no RT. These data imply that patients with extragonadal and extensive clinical Stage II seminoma now receive systemic chemotherapy as first line treatment, rather than as salvage therapy after relapse from RT.

Two additional facts may impact on response and survival statistics in future “advanced” disease studies. Adjuvant chemotherapy will not be used as frequently. A randomized trial in patients with pathological Stage II nonseminomatous GCT has shown that patients observed after RPLND with treatment with chemotherapy at relapse have similar survival when compared to patients undergoing RPLND followed by immediate adjuvant chemotherapy (17). This implies that, because of careful postoperative observation, patients would have minimal disease at relapse, usually at only one site (18). In addition, the awareness of GCT, by both practicing physicians and the public, will improve. The curability of GCT requires that the physician be vigilant, and articles appearing in the lay press (19) will educate the public. Better awareness leads to earlier diagnosis, and earlier diagnosis unquestionably leads to a better outcome because of treatment at a lower stage. This pattern is consonant with studies indicating that patients with locoregional disease (Stages I and II) have significantly shorter delays in diagnosis when compared to those patients presenting with Stage III disease (20).

These findings suggest that stage migration may be more prevalent than previously thought. The impact on the survival of patients with lung cancer has already been reported (2). Both improved technology and treatment result in shifts of patients from one treatment category to another. Single-arm trials which show higher response rates when compared to historical controls even from the same institution can be influenced by many factors. Stage migration is but one and is merely a subtle manifestation of an imbalance in prognostic variables, some of which might have been previously unknown. Changes in historical interpretation, new marker determinations, and better diagnostic tests can potentially bias statistical comparisons. For the present, the best solution is the properly stratified randomized clinical trial, which offers some protection against the subtle effects of stage migration.

REFERENCES

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