Predictive Value of Regression Rates following Chemotherapy of Small Cell Carcinoma of the Lung

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ABSTRACT

Tumor volumes measured at the time of initial therapy, during the 28 days following treatment, and following subsequent courses of therapy for 29 patients with small cell carcinoma of the lung were determined from serially measurable roentgenographic lesions. Tumor-halving times were calculated following initial therapy, and the proportions of pretreatment tumor volumes were evaluated within 28 days after initial therapy for 26 patients. Pretreatment tumor volumes ranged from 22.5 to 485 cu cm, with a median of 87 cu cm, a log mean of 83 cu cm, and a linear mean of 113 cu cm. The tumor-halving times ranged from 4 to 86 days, with a median of 12 days, a log mean of 12 days, and a linear mean of 16 days. The reduction of tumor volume expressed as a proportion of pretreatment volume following therapy ranged between 0.02 and 0.65, with a median value of 0.22, a log mean of 0.18, and a linear mean of 0.26. Using the linear mean of 0.26 as a discriminant for survival analysis, patients with <0.26 had a median duration of survival of 12 months, which was significantly longer (p = 0.035) than the median survival of 8 months for patients with >0.26. Tumor-halving time of 16 days was also able to separate the survival durations of 12 months of those <16 days compared to 8 months for >16 days (p = 0.0429). Tumor regression rate, determined from two consecutive tumor volume measurements, was correlated with the tumor volume (r = 0.677; p < 0.0001); and volume dependency of the tumor regression rate, as specified in Gompertzian kinetics, was demonstrated.

INTRODUCTION

The increasing use of intensive dose schedules, timed sequential administration of chemotherapy, and other therapeutic strategies based on tumor growth kinetics requires a more precise measurement of tumor growth and regression. Analysis of tumor growth and regression rates can provide the clinician with base-line information for assessing the course of the disease and efficacy of treatment in patients with cancer.

The dynamics of tumor behavior in patients with lung cancer have been described using serial chest X-ray measurements (9, 24). These have been related to response to therapy and survival. Slower-growing tumors have been found to have a better prognostic survival for future, while rapid growth, as in SCC, implies a greater responsiveness to therapy (7, 18, 19, 25, 27). Slower-growing tumors have been found to have a better prognosis for survival, while rapid growth, as in SCC, implies a greater responsiveness to therapy (7, 18, 19, 25, 27). These have been related to response to therapy and survival.

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The quantitative relationship between pretreatment tumor volumes and tumor regression rates was also quantitated by normalizing posttreatment tumor volumes with respect to pretreatment tumor volume. The tumor regression lines were generated based upon the normalized values of tumor volumes evaluated within 28 days after initiating therapy. When plateau levels were reached before 28 days, the regression lines were determined using the values obtained before reaching the plateau. These series of regression lines were utilized to make a quantitative assessment of therapeutic efficacy for each individual patient.

The quantitative relationship between pretreatment tumor volumes and tumor regression rate was examined, and it was related to whether tumor regression of SCC following therapy follows Gompertzian kinetics. Patient survival was calculated from the first day of therapy using the life table analysis method of Kaplan and Meier (17). The statistical significance of differences in survival between groups was tested using the generalized Wilcoxon test (13).

RESULTS

Tumor Volume and Regression Rates. Measurements of initial pretreatment tumor volumes utilizing chest X-ray films were made in a total of 40 patients with SCC. Twenty-nine of these patients met the criteria for evaluable. Twenty-six were studied serially (range, 3 to 18 measurements per patient) during their clinical course following therapy. Table 1 summarizes the results of tumor volume measurements, which include the determination of pretreatment tumor volume, tumor-halving time, and proportion of pretreatment tumor volumes following initial therapy. Survival from day of first treatment is indicated for each patient. Pretreatment tumor volumes ranged between 22 and 485 cu cm with a median of 87 cu cm, a log mean of 83 cu cm, and a linear mean of 113 cu cm.

The rates of tumor regression following therapy, expressed in terms of tumor halving time, were determined in 26 patients ranging between 4 and 66 days with a median of 12 days, a log mean of 12 days, and a linear mean of 16 days. The reduction of tumor volume was expressed as a proportion of pretreatment tumor volume evaluated within 28 days following therapy and ranged between 0.02 and 0.65 with a median of 0.22, a log mean of 0.18, and a linear mean of 0.26.

In order to investigate the prognostic value of tumor regression rates, the patients were divided into 2 groups, using the mean value of the proportion of treatment tumor volume (0.26) as a discriminant. Chart 1 shows the response to treatment of all patients as indicated by a plot of serial tumor measurements expressed as a proportion of pretreatment volume. Fifteen patients had a value of the proportion smaller than the discriminant (Chart 1A), and 11 patients had a value of the proportion larger than the discriminant value (Chart 1B). Although all patients treated had some degree of regression of their disease during the initial course of therapy, the time course of the proportions of the pretreatment tumor volume was variable among patients. In Chart 1A, all of the 15 patients had rapid reduction of tumor volume, but 4 of these responders had no significant change in tumor volume beyond 28 days after initiating therapy in spite of continuing cycles of chemotherapy.

Chart 2 shows the relationship between tumor regression rates and the tumor volume evaluated for 26 patients. It includes a total of 47 data points of which 24 were determined from 2 consecutive measurements immediately following initial chemotherapy and 23 from 2 consecutive measurements during subsequent courses of therapy. Tumor regression rate was calculated with respect to the log mean value of 2 serially determined tumor volumes.

The relationship illustrates that a retardation of tumor regression was significantly correlated with decreasing tumor volume, and this was quantitatively specified by Gompertzian kinetics with the correlation coefficient r = 0.677 (p < 0.0001) (3, 28). Volume dependency of the tumor regression rate B may be expressed by

\[ V = V_0 e^{-Bt} \]  

where \( V \) and \( V_0 \) are tumor volumes at time \( t \) and initial tumor volume, respectively. The rate of tumor regression \( R \) following therapy could then be calculated from the equation (26)

\[ R = \frac{1}{2} V_0 \]  

In Chart 2, all of the 15 patients had rapid reduction of tumor volume, but 4 of these responders had no significant change in tumor volume beyond 28 days after initiating therapy in spite of continuing cycles of chemotherapy.

In Chart 2A, all of the 15 patients had rapid reduction of tumor volume, but 4 of these responders had no significant change in tumor volume beyond 28 days after initiating therapy in spite of continuing cycles of chemotherapy.

Table 1  
<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Pretreatment volume (cu cm)</th>
<th>Halving time (days)</th>
<th>Proportion of pretreatment volume</th>
<th>Survival (mos.)</th>
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* Tumor volumes determined at the time of initial therapy.
SCC Regression Rates following Chemotherapy

Chart 1. Rates of tumor regression, expressed in terms of the proportion of pretreatment tumor volume, following initial therapy. •, responders; △, nonresponders; ■, progressors at the time of assessment. A, patients who had the proportion of pretreatment tumor volume determined within 28 days after therapy, less than the mean value (<0.266). B, patients who had the proportion of pretreatment tumor volume, larger than the mean value (>0.266).

B = R \ln \left( \frac{V}{V_0} \right)

where R is the retardation factor per day, and V₀ is the tumor volume at B = 0; in Chart 3, R = 0.023 per day, and V₀ = 5.54 cu cm.

Regression Rates and Survival. Evaluation of the pretreatment tumor volume in relation to survival using actuarial survival curves by the method of Kaplan and Meier (17), as illustrated in Chart 3A, indicates that the difference between the survival curves based on a discriminant of the mean tumor volume was not significant (p = 0.194). On the other hand, the proportion of pretreatment tumor volume was able to separate the survival curves based on a discriminant of the mean proportion (p = 0.035), as shown in Chart 3B. The survival durations determined by the tumor-halving time as a discriminant value also differed significantly (p = 0.043) and were illustrated in Chart 3C.

DISCUSSION

At The Johns Hopkins Oncology Center, an intensive induction chemotherapy regimen has been utilized for treating patients with SCC, which has resulted in an overall objective response rate of 78% and a complete response rate of 20% (2). These studies clearly indicate that complete regression of tumor is the major determinant of survival. Analyses of treatment failures in these studies reveal that the primary tumor in the lung is a major site of residual disease in patients with extensive as well as localized disease and is a major area of disease progression in patients who have had an initial response to treatment. Thus, an accurate quantitation of growth and regression of the primary
tumor should be of clinical value to provide base-line information necessary for the design of therapeutic regimens (4, 11, 12, 15, 16, 18, 27).

The growth rates of a variety of human solid tumors have been determined, and their relation to responsiveness to therapy and survival has been investigated (7, 8, 10, 19, 20, 25). Survival differences for patients with breast carcinoma have been shown to be associated with their growth rate, with rapidly growing tumors associated with a poor prognosis and more slowly growing tumors with a relatively favorable prognosis (5, 8). It has been reported that rapidly growing tumors are often responsive to therapy and that complete responders often remain disease free for extended periods of time after cessation of treatment. Disseminated, slowly growing tumors respond to therapy less often, and the responses are generally not durable. On the other hand, our previous study on the growth kinetics of SCC revealed that survival duration for patients with longer doubling time was significantly shorter than for those patients with shorter doubling time (19). These differences in growth rate and survival relationships may be explained by the higher responsiveness of SCC to initial chemotherapy compared to breast carcinoma.

The regression of SCC following intensive induction chemotherapy is related to patient survival in which survival for patients with rapid regression was significantly longer than for those with slow regression. This result appears to be largely attributable to higher responsiveness of SCC to initial therapy (1, 2, 14). Results similar to those of SCC have been reported previously, indicating that tumors with a short doubling time were more responsive to therapy and that a reduction in tumor volume was correlated with increase in survival (5, 7, 23, 25, 27). Actuarial survival curves generated by the method of Kaplan and Meier (17) showed that tumor regression rate separates the survival curves significantly (Chart 3, B and C). The magnitude of pretreatment volume was not effective in discriminatin the survival curves (Chart 34).

SCC has a faster growth rate and a higher growth fraction than other types of lung cancer, and a staging system based on local invasion of the primary tumor and of distant metastasis is used for clinical decisions. The relationship between the growth and regression kinetics of localized tumor and of distant metastasis has not been fully investigated in this tumor. Since the rate of growth and dissemination depends on host resistance as well as on the intrinsic kinetics of growth, variation can also be expected and has been found in the growth rate at different times in the same patient and for a primary lesion compared to a metastasis (8).

In the present study, we report the relations between tumor mass regression rate and survival in patients with SCC following an intensive induction chemotherapy. The time course of regression curves, expressed in terms of the proportion of pretreatment tumor volume (Chart 1) may be of value to provide a timely assessment of therapeutic efficacy and to allow for modification of doses and drug regimens. The slowing of the regression rate and appearance of plateau levels of regression curves following the initial induction therapy may be indicative of a reduced efficacy of the treatment or an increasing fraction of drug-resistant cell population and may provide a rationale for early intensification of chemotherapy or the use of a non-cross-resistant drug regimen.

In summary, the potential prognostic utility of the determination of tumor regression rate immediately after initiating therapy in SCC has been examined. This relationship may be of considerable clinical value to evaluate the efficacy of an induction chemotherapy regimen and to design subsequent courses of therapy. In addition, the observed volume dependency of tumor regression rate suggests that the regression of SCC follows Gompertzian kinetics. Further evaluation of these relationships in other cancers and following other treatment regimens is indicated as these observations may provide a guide to therapeutic decisions and provide an early indicator for changes in treatment intensity, drug regimen, and duration of treatment.

REFERENCES

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