EFFECT OF TREATMENT FOR HODGKIN'S DISEASE ON PULMONARY FUNCTION: RESULTS OF A PROSPECTIVE STUDY

BY

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EFFECT OF TREATMENT FOR HODGKIN'S DISEASE ON PULMONARY FUNCTION: RESULTS OF A PROSPECTIVE STUDY

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Running Head: Hodgkin's Disease - Treatment Effect on Pulmonary Function
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ABSTRACT

PURPOSE
Because each of very different treatments for Hodgkin’s disease may result in a high rate of cure, attention is currently focused on toxicity. This prospective study was designed to assess the effects of mediastinal irradiation and bleomycin chemotherapy on pulmonary function.

PATIENTS AND METHODS
Patients were treated from 1980 to 1990 on randomized controlled trials at Stanford University. Pulmonary function was tested prior to treatment (baseline), early after treatment (<15 months), and more than 36 months post-therapy.

Treatment options in the 145 patients studied included radiotherapy only or radiotherapy plus alkylating agent-based chemotherapy, radiotherapy plus bleomycin-containing chemotherapy or bleomycin-containing chemotherapy without radiotherapy. Treatments were grouped as I (mediastinal radiotherapy), II (mediastinal radiotherapy plus bleomycin) and III (bleomycin) for analyses of variance. A variety of regression models were employed to predict early and late effects on pulmonary function.

RESULTS
A decline in forced vital capacity (FVC) and diffusing capacity in the first 15 months after treatment followed by recovery after 36 months was observed for most patients. Patients receiving mediastinal radiotherapy had a more pronounced reduction in pulmonary function and less complete recovery. Linear regression identified baseline measurement as the only significant predictor of change in % predicted FVC or diffusing capacity; patients with higher baselines had greater decrements after therapy. Mantle radiotherapy was the only significant treatment variable, predictive of FVC and diffusing capacity within 15 months and FVC at 36 or more months. No patient has experienced pulmonary toxicity severe enough to require hospitalization. Overall, 32% of Group I patients (mediastinal radiotherapy), 37% of Group II (mediastinal radiotherapy plus bleomycin) and 19% of Group III had FVC values <80% predicted, while only 7% of patients had diffusing capacity <80% predicted three or more years after treatment.

CONCLUSION
This prospective analysis of pulmonary function after treatment for Hodgkin’s disease showed that mediastinal radiotherapy was the only significant treatment variable and that there were no significant interactions between mediastinal radiotherapy and bleomycin chemotherapy. The observed reduction in pulmonary function was mild, such that it would not be appropriate to alter treatment on the basis of these results. Rather, our results should be factored into the overall assessment of risk for morbidity and mortality for each of the potentially curative treatments for Hodgkin’s disease included in this study. As with all reports of late effects, these data should be interpreted with respect to the population tested, details of the treatment employed, methods of measurement and length of follow-up.
INTRODUCTION

Cardiac and pulmonary sequelae of treatment for Hodgkin's disease (HD) are of great concern given the ability to provide curative therapy to a majority of patients, many of whom are under thirty at the time of treatment (1). Pulmonary toxicity following mantle irradiation for HD has been variably reported, perhaps because of significant differences in technique and patient populations, (2-8). Bleomycin chemotherapy is associated with dose-related pulmonary toxicity, which may be enhanced by irradiation to the chest (9, 10). Given the expectation of prolonged survival for young people with HD, choices among available therapeutic alternatives are and ought to be made increasingly on the basis of late effects. These include sterility and an increased risk of acute leukemia, both of which are related to the cumulative dose of alkylating agent received in combination chemotherapy programs such as MOPP (mustard, vincristine, procarbazine, prednisone) (11-13). Second cancers, including breast and lung, and an increased risk of fatal coronary artery disease have been linked more recently to radiotherapy (RT) involving the chest (14-18). Adriamycin and bleomycin in the ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) regimen pose risks for late cardiopulmonary effects, which may be further potentiated by mantle RT (19-22).

Oncologists are developing strategies to reduce radiation exposure by utilizing "less toxic" chemotherapy for young patients with non-bulky, limited stage HD (23-24). If bleomycin is included in these newer regimens, it is paramount to evaluate the pulmonary effects in this very favorable population. Another clinical situation of concern involves young people who present with extensive intrathoracic HD, and therefore who are confronted with a choice of risking sterility or leukemia in the MOPP or MOPP/ABV(D) regimens; the uncertain cardiopulmonary toxicity of ABVD; or even MOPP/ABV(D), which may be potentiated by the necessary mantle RT (25-27). With these issues in mind we designed a series of randomized trials, conducted from 1980-
1990, in which acute and chronic toxicity were primary endpoints. Treatment effects on pulmonary function were addressed in a prospective manner in these studies (28).

PATIENTS AND METHODS

From 1980 to 1990 patients with an histologic diagnosis of Hodgkin's disease were invited to participate in a series of randomized controlled trials conducted at Stanford University. Treatment arms varied according to the extent of disease as detailed in Figure 1. Subtotal and total lymphoid RT include mantle irradiation as previously described (29). Six cycles of VBM (vinblastine, bleomycin, methotrexate) were given following involved field RT, which may or may not have included the mantle (23). PAVe (procarbazine, melphalan, vinblastine) or ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) chemotherapy were given for a total of six cycles, three before and three after mantle radiotherapy or a modified involved field in the case of subdiaphragmatic disease (28). Six cycles of PAVe and total lymphoid RT were administered in an alternating approach as previously described (28, 30). Patients treated with MOPP/ABVD received 12 cycles of chemotherapy. The planned dose of RT to the mediastinum was 4400 cGy administered in 150-200 cGy fractions with equal, daily anterior-posterior weighting. Patients with hilar adenopathy treated with RT alone and patients with extranodal extension to the pulmonary parenchyma received 1600 cGy RT to the lung with a 37% partial transmission block. The calculated cumulative dose for bleomycin in RT/VBM x 6, ABVD x 3 /RT/ ABVD x 3 and MOPP/ABVD x 12 was 120 u/m².

The treatments outlined in Figure 1 suggested that they could be grouped according to the potential pulmonary insult: Group I patients received mediastinal RT but no bleomycin; Group II patients received both mediastinal RT and bleomycin; while Group III patients received bleomycin without mediastinal RT. Patients treated with involved field RT + VBM were included in Group II if the mantle was included in the
involved field and Group III if it was not. Similarly, two patients with subdiaphragmatic bulky HD did not receive mantle RT. One received ABVD and was included in Group III, while the other patient was excluded as his treatment assignment, PAVe/modified involved field, included neither mediastinal RT or bleomycin. Figure 2 illustrates these groups and their component treatments.

As a major objective of these clinical trials was the assessment of toxicity, prospective pulmonary function testing was performed. Measurements were made as a baseline (before treatment), within 15 months of the conclusion of treatment, and >36 months after treatment. These time points were selected on the basis of our prior analysis in stage I and stage II patients and a large body of data indicating that measured pulmonary function declines during the first year after mediastinal RT with recovery at two to four years (2-8). Since involved field RT + VBM represented a novel therapy for a very favorable patient subgroup, pulmonary function was assessed during therapy in the first 10-20 patients. Pulmonary function testing was also conducted during treatment in patients receiving ABVD if they complained of cough or shortness of breath at any time. Bleomycin was discontinued if the % predicted diffusing capacity or FVC was less than 60-70. In order to standardize recovery from pulmonary toxicity, time was measured as the number of days or months elapsed following the last exposure to mediastinal RT or bleomycin chemotherapy.

All pulmonary function testing was performed in the clinical pulmonary function laboratory of the Division of Pulmonary and Critical Care Medicine at Stanford University Medical Center. Spirometric indices determinations of diffusing capacity were obtained from a computerized, watersealed volume displacement system (Collins DS-560, Braintree, MA), calibrated weekly. Spirometry was performed at least three times in each subject on every occasion, with at least two of the tests being within five percent of each other in value, as a measure of reproducibility. The technical features of the equipment and the method of test performance met or exceeded established American
Thoracic Society standards for spirometry (31). Determinations of diffusing capacity by
the single breath method, were done on each occasion in at least duplicate, with less than
five percent variability between values, again adhering to the American Thoracic Society
standards (32). Normal values for spirometry were based on population studies of Morris
et al. (33) and for diffusing capacity on values established by Bates et al. (34).

Standard statistical techniques were utilized, including regression and analysis of
variance (ANOVA). Computations were performed with BLSS (Berkeley Interactive
Statistical System) (35). One way ANOVAs were done to determine if the pulmonary
function of interest at <15 and >36 months following treatment differed across the
treatment groups described above. All patients were included in the ANOVAs at these
time points after comparisons of the empirical distribution of test results between the
entire group and those who also had a baseline measurement showed differences so small
by a number of criteria that we did not ascribe any p-values to them.

A variety of regression models were employed to predict outcomes at <15 and
>36 months. The selection of predictor variables was accomplished by "back-fitting" in
that models with large sets of predictors were reduced to those with fewer (36). This was
not done according to formal statistical criteria like cross-validation or Mallows' Cp (37).
Because of this "preprocessing" and because Gaussian assumptions may not be entirely
accurate, the reported significance levels (p-values) should be considered approximate,
although many are so small that this caveat does not apply.

RESULTS

Pulmonary function testing was performed on 145 patients. The characteristics of
119 patients tested after the completion of treatment are outlined in Table 1. The patients
were predominately young non-smokers and the incidence of prior lung disease
(e.g. asthma) was extremely low. The mean mid-mediastinal RT dose was the same in
Group I and Group II while the cumulative bleomycin dose was very slightly lower in
Group II than III. Five patients in Group II and two patients in Group III received less than 75% of the planned bleomycin dose. In the first 15 months after treatment, the most common changes from baseline studies included a reduction in diffusing capacity, vital capacity, forced expiratory volume in one second (FEV₁) and total lung capacity (TLC). The reduction in vital capacity was accompanied by a normal to increased FEV₁/forced vital capacity (FVC) ratio (mean observed: predicted = 1.03), consistent with a restrictive defect. We have elected to further describe the data only for FVC and diffusing capacity. Figure 3a illustrates FVC measurements for patients studied both at baseline and following treatment. Each line represents an individual patient. While there is a high degree of interpatient variability, there is consistency in the pattern of FVC measurement over time for each individual. Patients experience a reduction in FVC during the first year after treatment, followed by recovery at three or more years. The pattern for diffusing capacity (DLCO), described in Figure 3b, is very similar. There is a strong correlation (r = 0.899) between actual baseline FVC and FVC measured at 36 or more months after treatment, as is illustrated in Figure 4. All of these data represent the subgroup of patients for whom serial measurements are available.

Table 2 describes the ANOVA for the three treatment groups described above at baseline, < 15 months and > 36 months after treatment for the pulmonary functions FVC and DLCO. Data are presented as the mean percent predicted ± the standard deviation. The number of observations contributing to each mean are indicated in parentheses; they differ due to time constraints and the need for routine staging procedures prior to the onset of therapy. Thus, some patients did not have baseline studies while others have not been followed for a sufficient time period, failed therapy and received additional treatments, or did not comply with follow-up studies.

The baseline measurements are not different in the three groups. Measurements within 15 months of treatment significantly differ among the groups in that patients treated with bleomycin but no radiation (Group III) show no change to slight
improvement in FVC and DLCO. In contrast, Group I and II patients both have a reduction in FVC and DLCO within 15 months, and the decrement is more marked in Group II. The measurements at 36 months are more difficult to interpret due to fewer observations (for the reasons cited above). FVC measurements are highest for Group III followed by Group I and then Group II patients. These differences at 36+ months achieved statistical significance. Using the method of Bonferroni, the comparisons between individual groups are as follows: (I vs. III, p = 0.2; I vs. II, p = 0.1; II vs. III, p = 0.01) (38). No differences were seen among Group I patients who did or did not receive PAVe chemotherapy in addition to mantle RT at 15 and 36+ months. In contrast, DLCO measurements are generally excellent and not different among the groups.

Linear regression was applied with the goal of identifying predictors of change in present predicted FVC and DLCO at 36 or more months following treatment. Variables considered included age at treatment, gender, history of smoking, previous history of lung disease, height, total dose of mantle RT in cGy, total dose of lung RT in cGy (see definition above), cumulative dose of bleomycin, cumulative dose of doxorubicin and baseline measurement. Subsequent regressions were performed with additional covariates including interactions of the treatment variables and time. Baseline measurement proved to be the only significant predictor (p = 0.03 for FVC and 0.002 for DLCO, respectively); patients with higher baseline values have a greater decrement after therapy. This result is consistent with a large body of data describing regression toward the mean in untreated or placebo-treated subjects (39). However, in contrast to normal subjects, our HD patients may have baseline measurements compromised by mediastinal, parenchymal and pleural disease. Patients with lower baselines may demonstrate less change because the post-treatment measurements can reflect both improvement (related to efficacy of HD therapy) and decline due to pulmonary toxicity while patients with higher baselines may have greater decrements, reflecting pulmonary toxicity only. This is consistent with an early report by Evans et al. in which it is demonstrated that patients
with intrathoracic disease showed a marked increase in vital capacity and FEV₁, 0-2 months from the start of irradiation followed by a decrease at 2-6 months and gradual recovery (40). We obtained similar results in additional regressions, with the endpoints percent predicted FVC and DLCO at 36+ months in the patient population with both baseline and post-treatment tests, finding the baseline measurement to be the only independent variable of significance.

Further regressions were done with the entire population of patients tested within 15 months and greater than 36 months after treatment. The dependent variable in these regressions was percent predicted FVC or DLCO while the independent variables included only the treatments (bleomycin, doxorubicin, mantle RT and lung RT) and time. Table 3 illustrates these results. Mantle RT is very significant at 15 months and continues to be statistically significant at 36+ months for the dependent variable FVC % predicted. Mantle RT is significantly predictive for DLCO at 15 months but not at 36 months or beyond. Treatment interactions did not improve our ability to predict variability in any population and, in fact, detracted from the significance of mantle RT.

We also explored the effect of time above and beyond treatment effects within 15 months of treatment. Both time and its square are highly significant (p < 0.001) predictors of FVC and DLCO, indicating the incremental predictive power of time itself in the early evaluation of pulmonary effects.

None of the patients treated on the described clinical trials had acute pulmonary toxicity that required hospitalization. In some cases in which patients developed symptoms of cough or a measured drop in diffusing capacity during treatment to less than 70% of baseline occurred, bleomycin was discontinued prematurely. Several patients who were to receive 12 courses of MOPP/ABVD had treatment discontinued early because of poor tolerance during the final months. However, as previously mentioned, the cumulative dose of bleomycin was < 75% planned in just five Group II patients and two Group III patients.
For this analysis we reviewed all cases in which the pulmonary function values for FVC and DLCO were less than 80% of predicted at 36 months. This represented 18 of 62 (29%) observations for FVC and 7 of 92 (7%) observations for DLCO. Of the 18 "subnormal" FVC measurements, one was less than 60% (Group III patient), four were less than 70% (two Group I and two Group II patients), and the remainder fell between 70 and 80% predicted (six Group I, five Group II and two Group III patients). Stated another way, 32% of Group I patients, 37% of Group II patients and 19% of Group III patients had FVC measurements < 80% predicted three or more years after therapy. A 54 year-old Asian women with a body surface area of 1.3 had a DLCO of just 46% of that predicted following treatment with MOPP/ABVD; she is asymptomatic. Of interest, her baseline value was only 56%. Six other patients had DLCO values less than 80% (69, 72, 75, 75, 76, 76% predicted); four received RT without bleomycin and two received RT + bleomycin.

DISCUSSION

Radiation damage to the lungs is related to the volume of lung tissue irradiated, total dose, fractionation and the quality of the radiation. In typical mantle RT delivered for HD, the treated field includes the mediastinum and medial and upper parts of the lung while the shielded lung receives only a low level of radiation from internal scatter and transmission through the shields. Radiation affects both dividing and nondividing cells in the lung. Genetic damage to dividing cells involves the endothelial cells and type II pneumocytes while capillary endothelial and type I epithelial cells are most susceptible to nongenetic damage (41). Early (0-2 months) histopathologic changes include small vessel and capillary injury resulting in increased capillary permeability and alveolar exudates. Intermediate changes (2-9 months) include obstruction of capillaries by platelets, fibrin and collagen with hyperplasia of type II pneumocytes and infiltration of alveolar walls. Resolution is complete if the changes are mild or a chronic phase with
progression to fibrosis develops in more serious cases. Physiologic changes do not occur until about four to eight weeks after the completion of RT.

Two prospective studies of the effects of mantle RT on lung function have been published (6, 7). Smith et al reported on 30 patients in their prospective study, 16 of whom also received MOPP-like chemotherapy, with treatment administered in a split course technique. Twenty patients had baseline studies, while 14 patients had maximum follow-up for 73-118 months. Lung volumes dropped about 10% at 7-11 months and then returned to baseline at two to six years. Spirometry demonstrated a reduction to 90% predicted for FVC and FEV1 over the first 11 months after treatment, followed by a gradual increase to 100% predicted by two to four years. A gradual but progressive drop in FEV1/FVC after one year of follow-up was noted in smokers. DLCO values showed a similar pattern of slight early reduction followed by recovery to baseline. No consistent patterns were related to exposure to MOPP-like chemotherapy. Similarly, Shapiro et al. prospectively assessed 13 patients receiving mantle RT in doses ranging from 3700-4700 cGy and reported results with a maximum follow-up from 26-91 months (6). Vital capacity measurements were remarkably stable throughout the study. Total lung capacity was slightly lower in patients who presented with intrathoracic disease, but actual values were within 80-100% of predicted. These prospective studies, like many others, attempt to define late effects while facing the problems of small numbers, inconsistent follow-up and a variety of confounding clinical and treatment variables.

A relatively large number of retrospective studies have reported minor changes (5-10%) in lung volumes, usually of a temporary nature, up to 24 months after mantle RT treatment (2-5, 8). It is important to keep in mind that early studies or more recent ones with very long follow-up may reflect radiation techniques which have been significantly modified in respect to equipment, shielding technique, fraction size, anterior-posterior weighting and other technical aspects. Watchie et al. studied cardiopulmonary function in a group of 57 patients treated with mantle RT alone or in combination with MOPP
chemotherapy (8). Mean pulmonary function tests were normal. Patients with extensive intrathoracic HD had lower exercise tolerance as measured by peak oxygen consumption as did patients who had at least one lung irradiated by thin lung block technique. Morgan et al. evaluated 25 patients <35 years old treated 5-16 years earlier. They found a moderate decrease in diffusing capacity (72% predicted), which was significantly lower in the six patients who had also received MOPP (5). A large analysis of the Danish experience has been presented by Jensen et al. (42). They found that the number of patients with impaired lung function and/or complaints of dyspnea were similar in 54 patients treated with mantle RT, 26 patients treated with MOPP-like chemotherapy and 62 receiving combined modality therapy, followed a median of eight years from the end of treatment. Mantle RT was associated with obstructive and restrictive impairment while chemotherapy and combined modality recipients had a restrictive defect. This study is confounded by the significant tobacco exposure of the subjects (56% current smokers, 17% ex-smokers).

These authors went on to evaluate the influence of age and duration of therapy on lung function after mantle RT and MOPP chemotherapy (43). The 48 patients included in the study were divided into groups according to age at treatment (less than or greater than 30 years) and duration of follow-up (less than or greater than 8 years). The younger patients had a significantly greater restrictive lung function impairment and younger smokers had a significantly greater reduction in diffusing capacity and FEV₁ compared with older smokers. Duration of follow-up was not a critical factor in this study. Taken together, these data suggest that young patients may be more susceptible than older patients to both the pulmonary toxicity induced by irradiation and the additional adverse effects of tobacco smoke.

Age at treatment is of particular importance in pediatric HD where the prognosis is excellent, affording long term survival. Abnormal pulmonary function tests have been reported in six of 12 pediatric patients receiving 1950-5500 cGy mantle RT (and, in four
cases, MOPP-like chemotherapy) (44). In this small series, it was not possible to relate outcome to age at treatment or radiation dose. However, in children there is concern for decreased chest wall growth and decreased alveolar growth after mantle RT, such that most centers are employing only low dose RT or eliminating RT all together.

Bleomycin is recognized to cause pulmonary parenchymal damage. Several mechanisms that have been proposed including the formation of reactive oxygen metabolites resulting in fatty acid oxidation and membrane instability or inflammatory reactions (9). Direct lung injury through release of proteases and influx of leukocytes and increased collagen synthesis with subsequent pulmonary fibrosis have also been proposed (9, 41). The pathologic changes induced by bleomycin are not specific, rather they appear to be the common sequelae of primary injury to the alveolar epithelium and/or small vessels. These include an acute inflammatory infiltrate in the alveoli, interstitial and intra-alveolar edema, pulmonary hyaline membrane formation and interstitial and intra-alveolar fibrosis. The incidence of clinical bleomycin toxicity is related to dose (>450-500 u), age > 70 years, prior lung disease, concomitant RT, use of other cytotoxic agents and oxygen therapy. Decreased DLCO is seen in symptomatic patients. Despite the fact that the risk of pulmonary toxicity increases with doses greater than 450-500 u, severe pulmonary sequelae have been seen with total doses less than 100. With this profile, there is genuine concern that the combination of ABVD x 6 or VBM x 6 (total bleomycin dose 120 u/m2) and full dose mantle RT for HD may result in early or late pulmonary toxicity.

Santoro et al. reported on a series of 232 patients with HD who participated in a clinical trial in which they were randomized to receive six courses of MOPP or ABVD and RT in a split course design with subtotal or total lymphoid RT (19). Twenty per cent of the original group of ABVD/RT patients had delayed, severely reduced, or aborted chemotherapy due to myelosuppression compared with 60% of the MOPP group. The incidence of fatal radiation pneumonitis was the same (2.5% and 2.6%) in both groups.
Pulmonary function was analyzed retrospectively in 50 patients. No significant differences were noted in vital capacity, FEV$_1$, or DLCO. The differences between the mean values (MOPP/RT - ABVD/RT) were 6.5 (95% confidence intervals ± 8.8) for vital capacity and 9.1 (95% confidence intervals ± 11.1) for FEV$_1$. Parenchymal lung damage assessed radiographically was more common among ABVD patients (60% vs. 30%) and more severe. However, this did not translate to increased clinical toxicity.

These results are in contrast to a number of brief reports suggesting increased pulmonary toxicity of the ABVD/RT combination. LaGrange reported on five patients; all developed complications and there was one death (20). Differences in their treatment compared with Santoro et al. respectively, included RT dose (3600 cGy vs. 4000 cGy) and the timing of combined therapy (split course with subtotal/ total lymphoid RT vs. split course with mantle RT in four; sequential ABVD/RT in one). RT technique, including fractionation, was similar. All patients in the LaGrange report had massive mediastinal disease at onset. Cardiopulmonary toxicity after three courses of ABVD and mediastinal irradiation in 40 patients with favorable HD has been reported by Brice et al. (22). Total lung capacity (<80% predicted) was reduced in 17 patients and DLCO (<70% predicted) was low in eight patients evaluated a mean of 13 months after treatment. Increased pulmonary toxicity with ABVD x 6/RT and MOPP x 6/RT was preliminarily reported in the EORTC H6 trial (45). In both of these French studies, the fraction size was greater than 200 cGy.

Two groups have evaluated the pulmonary effects of ABVD/RT in the pediatric HD population. In a Children's Cancer Study Group protocol six of 58 patients (10%) receiving ABVD x 6 followed by low dose mantle RT (2100 cGy) developed grade 3 or 4 pulmonary toxicity (21). This included one of three receiving boost mantle RT (total dose 3800 cGy) and one of 11 patients receiving lung RT through a partial transmission block. A single pulmonary failure death occurred. In a report by Mefferd et al., 20 asymptomatic patients underwent pulmonary function testing 5 to 29 months after
treatment with alternating MOPP/ABVD x 6 and low dose (1500-2500 cGy) supradiaphragmatic RT (46). Six of the 11 had abnormal values for DLCO (mean 66%, range 58-80%), defined as a low absolute value or decrease from baseline, while eight of 20 had FEV1, FVC, TLC and flow volume loop measurements which indicated restrictive or obstructive disease.

In our manuscript we detail pulmonary function following treatment with mantle RT (alone or with PAVe chemotherapy), mantle RT and bleomycin chemotherapy (ABVD) and bleomycin chemotherapy (ABVD or VBM) without mantle RT. Minimal to modest pulmonary toxicity is seen at three or more years following any of the treatments employed. The ANOVAs describe a significant reduction in forced vital capacity, but not DLCO, among the three groups at three or more years. This is particularly notable when comparing the mantle RT + ABVD or RT + VBM and MOPP/ABVD groups. Regression analysis indicated that baseline measurement was the most significant predictor of pulmonary function at 36+ months; patients with higher baselines had a greater decrement. Several explanations may be offered for this finding, but the most intuitive is that the lower baselines are a reflection of intrathoracic disease in HD patients (40, 47). Mantle RT is a significant variable for both FVC and DLCO endpoints at 15 months and for FVC at 36+ months when regression is performed with consideration of treatment variables, a result consistent with the ANOVA. Treatment interactions (e.g. mantle RT x bleomycin) did not enhance the regression analyses. However, time itself has predictive value above and beyond treatment effects within 15 months following treatment.

These results encourage us that the ABVD/RT or RT/VBM combination is not associated with significant pulmonary toxicity compared with mantle RT alone or combined with PAVe chemotherapy. FVC is, however, slightly less than 80% predicted at 36+ months in about a third of patients managed with either treatment program. The least pulmonary toxicity was seen in patients receiving 12 courses of MOPP/ABVD without mantle RT. Factors which may influence the reporting of pulmonary effects after
HD treatment include the age and comorbid conditions of the patient population, prospective or retrospective nature of analysis, duration of follow-up, dose and schedule of bleomycin, dose and fractionation of mantle RT, dose and fractionation of lung RT, additional RT technique (use of blocks, anterior-posterior weighting, etc.), sequence of combined modality therapy if used, and number of observations made.

Our analysis suggests that mantle RT is the most significant treatment variable predictive of pulmonary function. It is of interest to recall that the series in which excess pulmonary toxicity was seen with ABVD/RT employed RT fractions greater than 200 cGy (22, 44). The influence of total mantle dose cannot be inferred from the data available in the adult population with HD, but this may be a consideration in the design of future studies. The sequence of chemotherapy/RT may also be of importance. There are some animal data which suggest that pulmonary toxicity may be enhanced when specific cytotoxic agents are introduced following vs. before RT; however, the data regarding bleomycin have been inconsistent in this regard (48).

While we cannot address this point in our study, we have elected a split course approach in patients with massive intrathoracic disease to minimize the likelihood of regrowth of HD during the last cycles of chemotherapy when resistance may be factor and dose and schedule of chemotherapy may be compromised. Currently, an intensive, abbreviated 12 week chemotherapy course followed by consolidative RT to 3600 cGy to bulky sites is being piloted in our institution.

Late follow-up at 10-15 or more years of pulmonary function in our patient population is desirable to complete the toxicity profile. At the time of this reporting, mantle RT is the treatment variable most predictive of mild reduction in FVC. While it would not be appropriate to alter treatment on the basis of these results, mantle RT is also the treatment variable associated with lung and breast cancer and cardiovascular morbidity (14-18). As the most effective and least toxic therapy is desired for all stages of HD, treatment approaches for early stage disease or massive intrathoracic disease
which reduce the dose or eliminate RT altogether are under investigation, very similar to
the current approach in pediatric HD. They will require very effective, relatively non-
toxic chemotherapy combinations. As for all treatments proposed for HD, these must
maintain the high rate of cure and require careful observation.
REFERENCES


37. Mallows C: Some comments on C_p. Technometrics 15:661-675, 1973


Table 1. Patient Characteristics

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Table 2. Pulmonary function according to treatment group

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<th>&gt;36 MONTHS</th>
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</thead>
<tbody>
<tr>
<td><strong>Mean % Predicted + S.D. (number of observations)</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>VITAL CAPACITY</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group I</td>
<td>91.5 ± 14 (50)</td>
<td>84.4 + 18 (39)</td>
<td>90.1 + 14 (25)</td>
</tr>
<tr>
<td>Group II</td>
<td>88.5 ± 16 (29)</td>
<td>70.0 + 16 (34)</td>
<td>80.4 + 13 (19)</td>
</tr>
<tr>
<td>Group III</td>
<td>91.8 + 16 (29)</td>
<td>97.7 + 18 (32)</td>
<td>96.7 + 15 (16)</td>
</tr>
<tr>
<td></td>
<td>( p = 0.625 )</td>
<td>( p &lt; 0.001 )</td>
<td>( p = 0.003 )</td>
</tr>
<tr>
<td><strong>DIFFUSING CAPACITY</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group I</td>
<td>107.7 + 21 (46)</td>
<td>97.4 + 24 (35)</td>
<td>97.7 + 16 (26)</td>
</tr>
<tr>
<td>Group II</td>
<td>111.0 + 23 (28)</td>
<td>83.8 + 21 (32)</td>
<td>108.8 + 19 (20)</td>
</tr>
<tr>
<td>Group III</td>
<td>108.0 + 22 (29)</td>
<td>108.4 + 26 (32)</td>
<td>103.5 + 24 (16)</td>
</tr>
<tr>
<td></td>
<td>( p = 0.800 )</td>
<td>( p = 0.004 )</td>
<td>( p = 0.624 )</td>
</tr>
</tbody>
</table>
Table 3. Regression analyses for % predicted FVC and DLCO

<table>
<thead>
<tr>
<th></th>
<th>15 MONTHS</th>
<th>36 MONTHS</th>
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<tbody>
<tr>
<td></td>
<td>n=105</td>
<td>n=60</td>
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<tr>
<td><strong>VITAL CAPACITY</strong></td>
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</tr>
<tr>
<td>Lung RT</td>
<td>0.51</td>
<td>0.29</td>
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<tr>
<td>Mantle RT</td>
<td>&lt;&lt; 0.01</td>
<td>0.01</td>
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<tr>
<td>Adriamycin</td>
<td>0.36</td>
<td>0.73</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>0.09</td>
<td>0.26</td>
</tr>
<tr>
<td>Multiple R-squared</td>
<td>0.25</td>
<td>0.16</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>15 MONTHS</th>
<th>36 MONTHS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=99</td>
<td>n=62</td>
</tr>
<tr>
<td><strong>DIFFUSING CAPACITY</strong></td>
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<td></td>
</tr>
<tr>
<td>Lung RT</td>
<td>0.38</td>
<td>0.43</td>
</tr>
<tr>
<td>Mantle RT</td>
<td>&lt;0.01</td>
<td>0.66</td>
</tr>
<tr>
<td>Adriamycin</td>
<td>0.10</td>
<td>0.91</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>0.68</td>
<td>0.15</td>
</tr>
<tr>
<td>Multiple R-squared</td>
<td>0.16</td>
<td>0.06</td>
</tr>
</tbody>
</table>
FIGURE LEGENDS

1. Treatments for Hodgkin's disease according to stage in the Stanford randomized clinical trials 1980-88.

2. Three treatment groups according to category of potential pulmonary toxicity.

3a. Forced vital capacity measured serially in 37 patients. Zero time refers to the pre-treatment measurement and all other times are measured after the last treatment with either mantle RT or bleomycin. Each line represents an individual patient.

3b. Diffusing capacity measured serially as above (n = 31).

4. Correlation between baseline FVC and FVC measured at 36 months or more after the completion of mantle RT or bleomycin.
Figure 1

Diagram:
- MOPP/ABVD
  - N1B, IV
  - Extensive splenic (PS IIIA)
- PAVE/Total Lymphoid RT
- ABD/Moddied Involved Field RT
  - Bulky "CS I-II A/B, III A"
- PAVE/Moddied Involved Field RT
- Involved Field RT + VBM
  - "Favorable" (PS I-II A/B, III A)
- Subtotal/Total Lymphoid RT
Figure 2

**Involved Field did not include mantle irradiation**

See text for description.

MOPP/ABVD
ABVD/Modifled Involved Field Irradiation
Involved Field Irradiation + VBM

**Group III**

Bleomycin - no mediastinal irradiation

Mediastinal Irradiation + bleomycin

**Group II**

PAVE/Total Lymphoid Irradiation
PAVE/Modifled Involved Field Irradiation
Supraclavicular Total Lymphoid Irradiation

**Group I**

Mediastinal Irradiation - no bleomycin
Figure 3a

Percent Predicted

Months

0

20

40

60

80

100

40

60

80

100

120

140
36 months (liters)