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Long-Term Pulmonary Toxicity of Multiagent Chemotherapy Including Bleomycin and Cyclophosphamide in Osteosarcoma Survivors

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Purpose: To assess long-term pulmonary effects of multiagent chemotherapy, we studied serial pulmonary function tests (PFTs) of 35 children with osteosarcoma up to 12 years after diagnosis.

Patients and Methods: We analyzed 84 sets of PFTs from 35 patients diagnosed with osteosarcoma between 1981 and 1991. They received bleomycin, cyclophosphamide, methotrexate, doxorubicin, cisplatin, and actinomycin D over 9–12 months and we performed PFTs from 3 days to 152 months after diagnosis. Time period I included 36 PFTs (43%) performed between 1 and 5 months from diagnosis, time period II included 20 PFTs (24%) performed between 8 and 12 months from diagnosis, and time period III included 28 PFTs (33%) performed between 12 and 119 months from diagnosis.

Total lung capacity (TLC), forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and carbon monoxide diffusing capacity (DLCO) were analyzed. Maximal respiratory pressures and arterial blood gases were measured to assess muscle weakness and gas exchange, respectively. Mean differences in PFTs were compared among the three time periods and between time period pairs.

Results: All mean PFT values showed significant differences among time periods. Significant decline in DLCO; ($P = .012$), TLC ($P = .020$), and FEV1 ($P = .028$) between time periods I and II were noted followed by a trend towards recovery between time periods II and III. Time periods I and III were not significantly different from one another. Mean PFTs performed after 2 years of diagnosis were not different from mean PFTs performed from diagnosis to 2 years.

Conclusion: This dosage regimen of multiagent chemotherapy for osteosarcoma patients caused a transient, but significant, decline in PFTs within 8–12 months after administration but appears to cause no significant long-term pulmonary function abnormalities.

Key words: pulmonary toxicity, chemotherapy, osteosarcoma, bleomycin toxicity, cyclophosphamide toxicity, pulmonary function after chemotherapy

INTRODUCTION

Most chemotherapeutic agents given either singly or in combination have been reported to cause significant pulmonary toxicity [1–3]. We analyzed pulmonary function tests (PFTs) in children with osteosarcoma who were treated with a regimen of multiagent chemotherapy, including bleomycin, to determine long-term sequelae of chemotherapy on lung function. Unlike acute pulmonary bleomycin toxicity, long-term pulmonary effects of multiagent chemotherapy including bleomycin in children are not known. With improving survival rates, it is projected that by the year 2000, 0.1% of all adults would be survivors of childhood cancer. Hence, long-term pulmonary effects of chemotherapy may influence subsequent pulmonary morbidity, exercise tolerance, and quality of life in adulthood.

PATIENTS AND METHODS

Between 1981 and 1991, 44 newly diagnosed nonmetastatic patients and one newly diagnosed metastatic patient with osteosarcoma were treated on two sequential chemotherapy trials of combination chemotherapy over a 9–12-month period consisting of the following drugs and cumulative doses [4]: bleomycin (120–150 mg/m^2), cyclophosphamide (6,000 mg/m^2), high-dose methotrexate (144 g/m^2) with leucovorin rescue, doxorubicin (380–390 mg/m^2), cisplatin (400–480 mg/m^2), and actinomycin D (6 mg/m^2). Figure 1 shows the POG 8107 chemotherapy regimen involving immediate surgery followed by adjuvant chemotherapy [5]. POG 8651 chemotherapy regimen involves either presurgical chemotherapy with surgery performed on the 10th week or immediate surgery followed by 44 weeks of chemotherapy [6].

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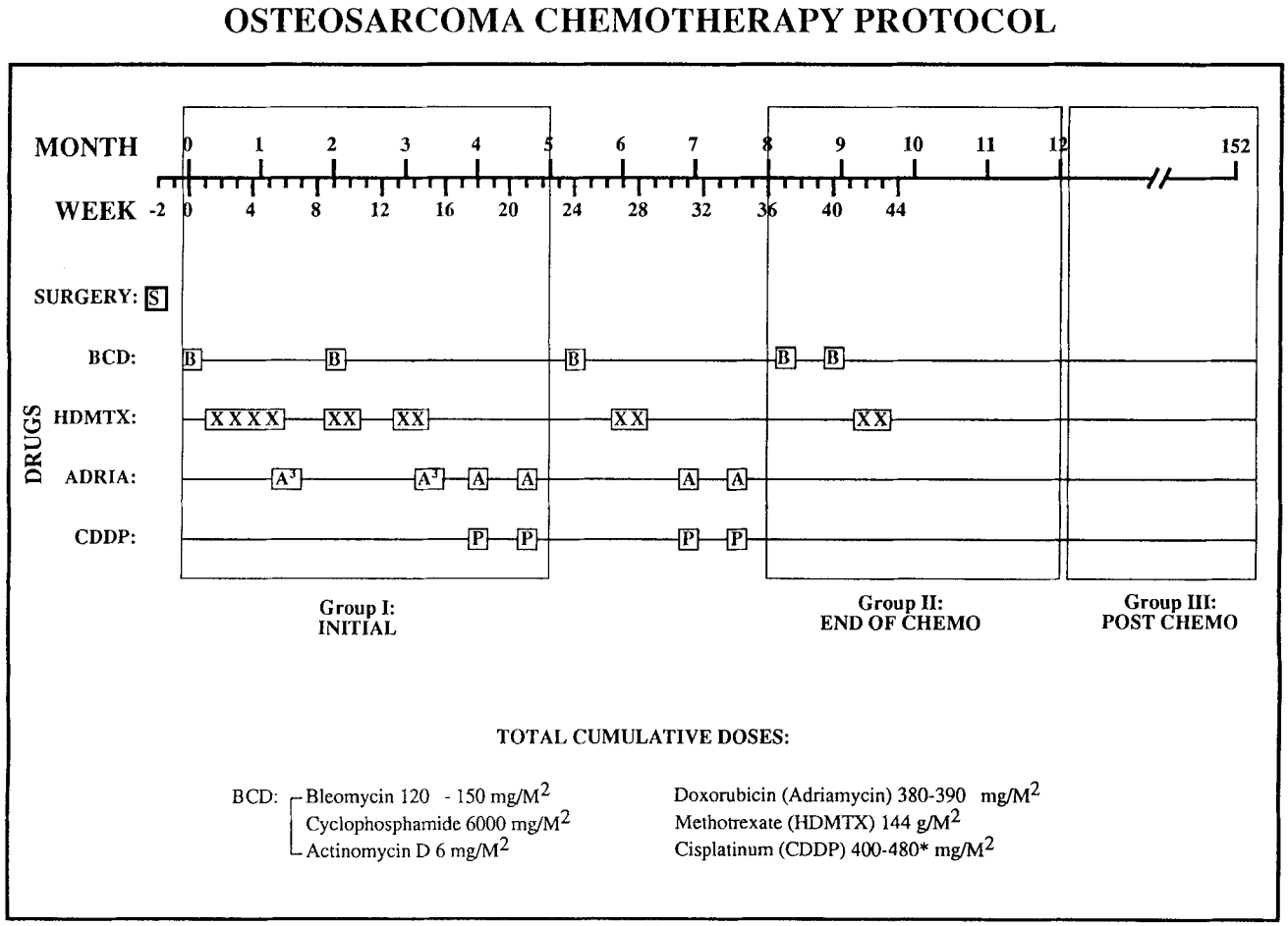

Fig. 1. This diagram shows chemotherapeutic protocol POG 8107 consisting of surgery performed on diagnosis followed by 44 weeks of chemotherapy. The study time period groups when PFTs were analyzed are shown in relation to the protocol [5].

Of the 45 patients with osteosarcoma, PFT data were available for 35 (78%). All patients with at least one set of PFT were recalled for repeat testing. Mean age for this group was 13.3 years (range 4.4–18.3 years) at diagnosis.

Forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1) were measured and expressed as means of percentages of predicted values based on height or armspan as described by Knudson et al. [7]. Total lung capacity (TLC) and lung volumes were measured by body plethysmography [8,9] and compared to the values of Cook and Hamann [10]. Carbon monoxide diffusing capacity by single breath diffusion technique (DLCO) was measured following standard techniques and corrected for hemoglobin and alveolar volume [11]. Normal values are between 80 to 120% of predicted, and a decrease in predicted value represents deterioration in pulmonary function. To determine the degree of muscle weakness, maximal inspiratory and expiratory pressures (cm H_2O) were measured using wall-mounted diaphragm gauges connected to a mouthpiece [12]. Arterial blood gases (ABG) were drawn to assess gas exchange. Radiographic abnormalities were recorded from chart reviews. Standard American Thoracic Society (ATS) questionnaires [13] were sent to all patients with PFT data and who completed chemotherapy more than 5 years ago to determine residual respiratory symptoms.

A total of 84 sets of PFTs were available on 35 patients. Single sets of PFTs were analyzed from 15 patients and multiple sets were analyzed from 20 patients (69 tests). Time period I represents 36 tests (43%) from 32 patients performed between 1 and 5 months following diagnosis. Time period II represents 20 PFTs (24%) from nine patients performed between 8 and 12 months after diagnosis. Time period III represents 28 PFTs (33%) from nine patients performed between 1 and 2 years after diagnosis. Six patients performed PFTs in all three time periods (33 tests). All PFTs obtained 2 or more years after diagnosis were also compared to those obtained less than 2 years after diagnosis to determine long-term deterioration in PFTs after chemotherapy has been completed.

Since only 6 of 35 patients performed PFTs in all three time periods, we carefully examined the data to make

sure that using all subjects in our analyses does not give biased results. We found very little apparent bias. In fact, the results were almost identical using all patients vs. only the six. Further, the *P* values using all patients were slightly more conservative (larger) than the *P* values using only the six observed during all three time periods. Although only six patients were observed in the latter analysis, *P* values were smaller because the responses within a time period for these six subjects were very similar, whereas adding all patients to the analysis added more variability, resulting in larger *P* values.

Because no apparent bias was found using all patients, differences in time period means and the significance of these differences were calculated using the method of Liang and Zeger [14], which uses all patients available in a given time period. Because of the relatively small sample size (35 subjects), the *P* values were calculated by comparing the Liang and Zeger test statistics to a t-distribution with 32 degrees of freedom (35 subjects minus three degrees of freedom for estimating the time period means). These test statistics for differences in pairs of time period means are very similar to paired t-tests. The Bonferroni correction was applied for multiplicity of tests. For a given PFT, differences with a *P* value less than .05/3 = 0.0167 were considered significant. Using the Liang and Zeger method, observations on the same subject in a given time period are given less weight than observations in different time periods. Thus, for a given PFT, the method uses one value per subject for a given time period, and that value is the mean of the observations during that time period.

RESULTS

Thirty-five patients were referred for PFTs at various times during their clinical course after diagnosis of osteosarcoma as suggested by protocol or because they were considered by their oncologists to be at high risk for developing pulmonary complications based on abnormal clinical and radiologic features. Of these, 7 (20%) had normal chest imaging studies (x-ray or chest computed tomography), 23 (66%) had abnormal chest imaging studies, and 5 (14%) had no chest imaging available. The abnormalities noted at different time points consisted of one or more of the following: pulmonary metastases (7), nodular fibrosis (10), and transient infiltrates or atelectasis (6). Nine patients with abnormal imaging studies (9 of 23) had thoracotomy for biopsies or resection. Of these, 4 had tumor metastases and 5 had nodular fibroses. All resections involved subsegments of lung insufficient to account for a reduction in measurable lung volumes. Only one patient presented with diffuse metastatic disease on diagnosis. Other abnormalities associated with nodular lesions included pulmonary edema, pleural effusion, and spontaneous pneumothorax. Patients were not tested during the perioperative period or during acute illness.

To determine whether progressive disease and subsequent mortality contributed to decline in PFTs in each time period, the timing of death and causes were examined. Six (17%) patients died during the study period. Five of six died of progressive disease and one died of cardiovascular collapse secondary to a ruptured aneurysm. Three of six died after the time period I with only one set of PFTs performed on diagnosis. Three of six died 1–12 years after diagnosis (time period III). Of these three, one patient died 14 months after diagnosis but only had a single set of PFTs performed on diagnosis, one patient died of metastatic disease 5.5 years after diagnosis (2.5 years after the last PFT), and one patient died 4 years after diagnosis (9 months after the last PFT) from a ruptured subclavian aneurysm.

Within time period I, 16 PFTs performed before chemotherapy were compared with 20 PFTs performed after chemotherapy was started. Although individual changes cannot be assessed retrospectively, when analyzed separately, the group studied prior to the first dose of drug had no difference in mean PFT values compared to those studied after the first dose.

Figure 2 shows means of percent predicted for TLC, FVC, FEV1, and DLCO plotted for each time period group. Time period I corresponds with the beginning of chemotherapy, time period II falls within 8–12 months after initiation of chemotherapy, and time period III falls within 1–2 years after chemotherapy. It shows a significant decline from I to II and a trend towards recovery from II to III. Table I shows that mean PFT values for TLC, FVC, FEV1, and DLCO declined 10% at the end of chemotherapy (I vs. II) followed by a 3% recovery after completion of chemotherapy (II vs. III). The differences among the means for the three groups were significant for TLC, FVC, FEV1, and DLCO.

Comparison between time period group pairs (Table II) shows a significant decline in DLCO ($P = 0.012$), TLC ($P = 0.020$), and FEV1 ($P = 0.028$) between time period groups I and II. Differences between time period groups II and III were not significant. The overall difference between time period groups I and III was not significant for TLC ($P = .066$), FVC ($P = .137$), and DLCO ($P = .121$). FEV1 was the only parameter that was significantly reduced between time period groups I and III (Table II, $P = 0.038$).

DLCO showed the most significant decline between time periods I and II (Table II; $P = 0.012$) and the most significant difference among time period groups (Table I; $P = 0.002$). Using an overall 0.05 significance level for each type of PFT and applying a Bonferroni correction, only DLCO meets the significance value of 0.017.

PFTs performed before and after 2 years of diagnosis (Table III) were not significantly different. Muscle weak-

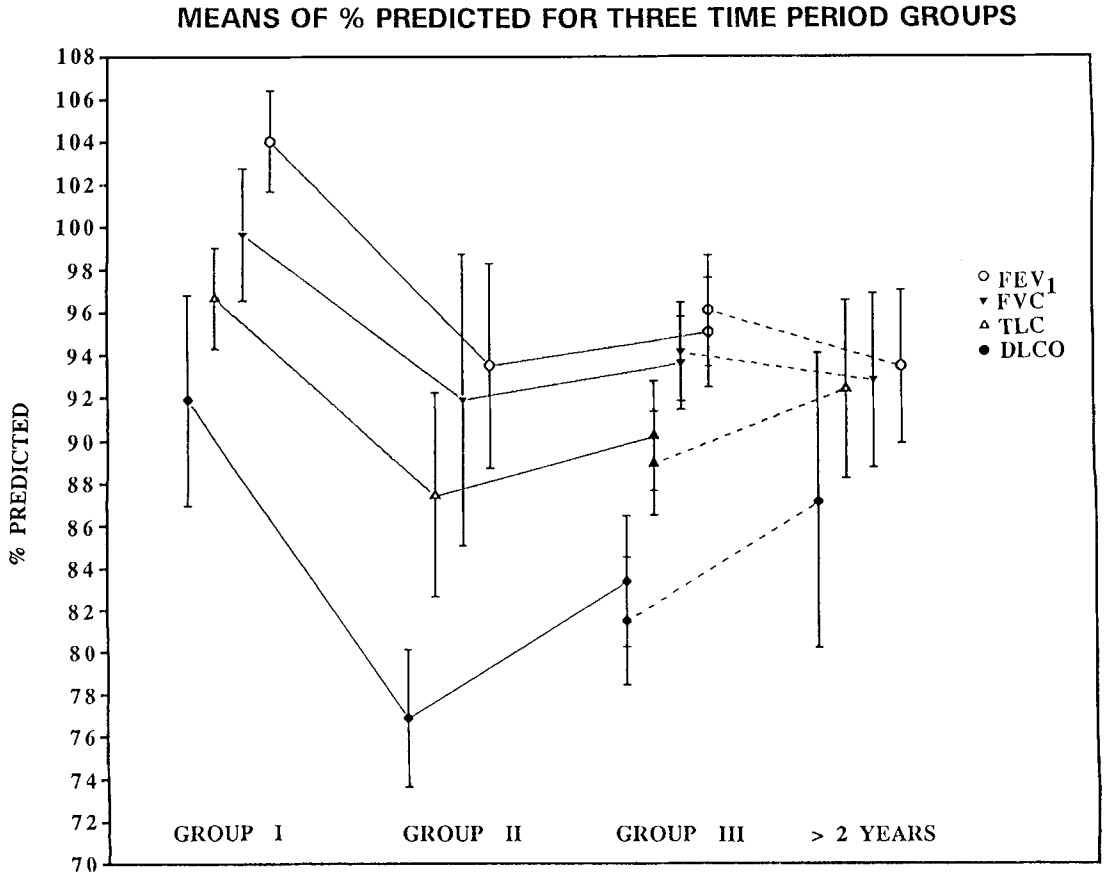

Fig. 2. Line graph shows the means of percent predicted for each PFT measure for each study group. It shows a decline of FEV1, FVC, TLC, and DLCO from time period I to II and a trend towards recovery from time period II to III. Time period III was further subdivided into tests done within the first 2 years from diagnosis and those done after 2 years from diagnosis. These points were not significantly different.

TABLE I. PFTs (Percent Predicted)*

PFT	Group I (n = 32)	Group II (n = 9)	Group III (n = 9)	*P*
TLC	96.66 ± 2.36	87.44 ± 4.78	90.22 ± 2.55	.009
FVC	99.64 ± 3.11	91.90 ± 6.81	93.61 ± 2.18	.038
FEV1	104.03 ± 3.53	93.50 ± 7.11	95.04 ± 2.12	.001
DLCO	91.88 ± 4.92	76.88 ± 3.24	83.38 ± 3.10	.002
MIP/MEP	108/120	103/124	115/142	

*Group I = 36 PFTs; group II = 20 PFTs; group III = 28 PFTs. Values shown are means ± SE.

TABLE II. Comparing Group Pairs (*P* Values Using t Test)

PFT	I:II	II:III	I:III
TLC	.020	.546	.066
FVC	.085	.801	.137
FEV1	.028	.823	.038
DLCO	.012	.067	.121

ness or gas exchange abnormalities were not evident by maximal respiratory pressures and ABG determination.

Standard ATS pulmonary symptom questionnaires were obtained from patients who completed chemotherapy at least 5 years ago. Of 18 respondents, 20% had a productive cough about four to six times throughout the day. Thirty-eight percent had chest colds associated with wheezing. These findings are not significantly different from the general adult population.

DISCUSSION

Osteogenic sarcoma is the most common malignant bone tumor in adolescents and involves areas of most

TABLE III. PFTs 12–24 Months Compared With PFTs After 24 Months

PFT	N	≤ 24 Months ± SE	N	> 24 Months ± SE	*P*
TLC	17	88.94 ± 2.42	8	92.40 ± 4.15	.467
FVC	17	94.12 ± 2.30	9	92.82 ± 4.04	.768
FEV1	17	96.06 ± 2.58	9	93.45 ± 3.57	.536
DLCO	14	81.50 ± 3.05	6	87.14 ± 6.92	.394

rapid bone growth [15]. Since the lungs are not primarily affected, abnormalities in pulmonary function are likely attributable to chemotherapy in the absence of pulmonary metastasis.

To determine whether chemotherapy causes long-term changes in pulmonary function in children, we reviewed PFTs over a 12-year period from 35 patients diagnosed with osteosarcoma between the ages of 4–18 years. We observed a decline in pulmonary function from 1 to 12 months after diagnosis which includes a 9–12-month period of chemotherapy, followed by a recovery observed between 1 and 12 years after completion of chemotherapy.

In adults, bleomycin doses greater than 400 units have been associated with increased incidence of pulmonary fibrosis. Although bleomycin toxicity is reported at low doses, the incidence of toxicity increased from 5% to 17% at doses above 550 units [16]. Similar rates of interstitial pneumonitis have been reported when bleomycin was used in combination with doxorubicin, cyclophosphamide, cisplatin, and methotrexate [17].

Pulmonary toxicity secondary to bleomycin is characterized by a restrictive ventilatory defect with decreased lung volumes and DLCO [18]. Protocol guidelines suggest decreasing bleomycin doses when DLCO falls to less than 65% of pretreatment values [19]. As such, DLCOs are commonly used as indicators for subclinical lung damage in asymptomatic patients.

Pulmonary toxicity secondary to cytotoxic agents is characterized by diffuse collagenosis and irreversible fibrosis. Histopathologic findings include an initial phase of vascular injury with impairment of endothelial cell function. This is followed by type II pneumocyte proliferation and cellular atypia, cellular infiltration, and recruitment of fibroblasts characterizing the phase of chronic inflammation [20]. Drugs such as cyclophosphamide cause direct injury resulting in sclerosing alveolitis and depletion of hepatic glutathione stores, predisposing the lung to oxidant injury. Methotrexate causes injury by a hypersensitivity mechanism or anaphylaxis followed by chronic injury with inflammation [1].

The effect of high concentrations of cytotoxic agents presented to the alveolar capillary bed during different stages of lung growth is unknown. Lung growth is maximal from birth to 2 years and continues through 8 years old, after which less than 5% increase in alveolar numbers are observed [21]. However, an increase in alveolar size continues with linear growth into adulthood [22].

The present study included only five patients less than 8 years old on diagnosis. As a group, these patients had normal PFTs for height and had no height retardation which may affect predicted values for PFTs.

Wohl and colleagues [23] studied pulmonary function in 20 children treated for Wilms tumor with both irradiation and chemotherapy. Their results show a reduction in lung volumes in all patients treated with pulmonary irradiation and actinomycin D when tested 7–14 years after initial tumor treatment. However, the patients who had no pulmonary metastasis who received only actinomycin D without pulmonary irradiation had normal lung volumes in the same time period. Ellis et al. [24] studied a group of 28 patients with nonmetastatic osteosarcoma (mean age 19 years) who were treated with irradiation and doxorubicin. They observed a 15% decline in FVC, FEV1, and DLCO 6 months after chemotherapy, with a return to baseline by the second year which was maintained up to 5 years after chemotherapy. TLC and functional residual capacity decreased at 6–12 months but did not recover over the 5-year follow up. Although restrictive lung disease after total lung irradiation is well established, the long-term pulmonary effects of chemotherapeutic agents alone are not well described. Studies in adults with metastatic testicular carcinoma who survived the acute episode of bleomycin-induced pneumonitis demonstrate a reduction in flows (FVC) and DLCO which is completely reversible within 2 years [25].

Previous studies questioned the accuracy of PFTs done during chemotherapy due to confounding factors [26] such as muscle weakness, poor effort, and/or overall poor state of health which may falsely lower measurements of effort-dependent tests such as FVC and FEV1. In this study, all tests fulfilled ATS standards for reproducibility. No patient was tested during an active pulmonary illness, or when discomfort or pain may have interfered with the quality of the study. This was supported by values obtained for maximal respiratory pressures which showed no significant muscle weakness. Neither anemia, which is common in patients receiving chemotherapy, nor low lung volumes secondary to muscle weakness falsely lowered our DLCO results [27]. Despite the fact that DLCO had the highest coefficient of variation, this test showed the most significant differences among groups. This is similar to previous reports in patients with bleomycin toxicity. Hence, it has been suggested that decrements in

DLCO during chemotherapy may be indicative of subclinical lung damage [17].

Although studies suggest that decline in PFT may not correlate with clinically or radiographically evident lung disease [1], a decline of 10–15% in predicted values from a normal baseline may still fall within the normal range, but may represent a significant deterioration in lung function in patients receiving chemotherapy. Whether this decline is a marker of transient vascular inflammation or precedes clinically evident pulmonary fibrosis may be difficult to ascertain.

No long-term abnormalities in PFT, gas exchange, and symptomatology were associated with this regimen. The deaths of three patients between 8 and 12 months after diagnosis did not affect PFT values for time period II since all three patients had only performed a single set of initial PFTs. It is also unlikely that the death of three patients in time period III affected the mean PFT values for that time period since two deaths occurred 9 months and 30 months after the last PFT was performed and one had only a single study. In the first case, the PFTs for time period III were unchanged and improved compared to the patients' PFTs at time period I.

The biopsy finding of benign pulmonary nodules and fibrosis on diagnosis in 4 of 23 (17%) patients who had abnormal chest imaging is consistent with the NCI report that 3 of 19 (16%) patients with Ewings sarcoma had benign pulmonary nodules [28]. Biopsy-proven benign pulmonary nodules are not an unusual finding in patients with osteosarcoma. These have been reported on initial diagnosis and during chemotherapy. The etiology of these nodules is varied. Fibrotic nodules may result from acute inflammation or infectious granulomas, may be due to the effects of bleomycin therapy or irradiation, or may represent old metastatic lesions that may have been treated [29].

Symptoms of airway reactivity reported on the questionnaire well after completion of chemotherapy are not supported by PFT data. The decline in FEV1 noted between time periods I and III is not consistent with obstructive airways disease since the FEV1/FVC ratio was normal and unchanged for all three groups. However, because of the small sample size, the power to detect differences between groups was small. Also, the absence of obstructive PFT changes may be because the patients were not tested during the episodes of chest colds and wheezing. The suggestion of airway reactivity by clinical symptoms without alteration in FEV1/FVC ratio may be better investigated by performing a cold air or methacholine challenge along with a more detailed examination of family history for airway reactivity. All patients denied exercise intolerance. However, exercise endurance and maximal exercise capacity, which are more sensitive indices of pulmonary reserve, are better assessed by an exercise study. Also, the range of voluntary activity in these patients is large with some limitation in activity attributable to leg amputation (19 of 35) or leg length discrepancy.

CONCLUSIONS

This dosage regimen of bleomycin, cyclophosphamide, high-dose methotrexate with leucovorin rescue, doxorubicin, cisplatin, and actinomycin D for osteosarcoma appears to cause no significant long-term pulmonary abnormalities in children and young adults. There was a significant decline in pulmonary function most sensitively measured by DLCO 8–12 months after starting chemotherapy with recovery within the next 12 months. No further change in pulmonary function was noted beyond 2 years after chemotherapy. Maximal respiratory pressures and ABG remained normal 2 years after chemotherapy.

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