for acute leukemia. The incidence of pneumonitis related to irradiation in these patients is not known with certainty; however, "idiopathic" interstitial pneumonitis has been reported to occur in as many as 35% of patients with a mortality rate of 10 to 24% depending on presence of associated risk factors (use of methotrexate, age, presence of severe graft vs. host disease, interval from diagnosis to transplantation, performance status pre-transplant, radiation post-transplant associated with methotrexate administration) (16,17). With respect to upper half-body irradiation, there are now considerable data which bear on the question of lung tolerance in humans (18-22). If a single uncorrected dose of 800 rad is employed, the incidence of an acute, generally fatal radiation pneumonitis syndrome has been reported as 29% in a series of patients with long-term follow-up (18). As a function of absolute dose to the lung the onset of radiation pneumonitis occurs at about 750 rad with a 5% to 9% incidence at approximately 820 rad (21,22). The peak incidence is 2 to 3 months after irradiation with a time of onset ranging from 1 to 7 months. In our initial study, a single fraction of 800 rad (8 Gy) was used corrected for lung inhomogeneity calculated using chest computed tomography for total body irradiation (23).

Unfortunately, fatal radiation pneumonitis was observed in both evaluated patients treated with this protocol at the FHCRC. Similarly, patients given unmodified autologous marrow at the University of Washington treated with an identical chemoradiotherapy protocol suffered radiation pneumonitis.

A combination of high-dose Bu and Cy followed by marrow transplantation has been shown to be effective therapy for a variety of hematological malignancies including acute nonlymphocytic leukemia and chronic myelogenous leukemia. Because alkylating agents are effective drugs in the treatment of breast cancer, combinations of high-dose alkylators may prove particularly efficacious in the therapy of breast cancer. Since high doses of Bu and Cy are marrow ablative, hematologic recovery will only occur after marrow transplantation.

Four patients with metastatic breast cancer have been treated on FHCRC protocol 348 with the Bu/Cy regimen followed by autologous marrow transplantation (AMT). One patient died of bacteremia 17 days post- transplant. Two patients died of pulmonary hemorrhage both on day 14 post transplant. The fourth patient, who had liver, bone and marrow disease achieved a complete response but died of disseminated Aspergillus infection 306 days post transplant. Of interest, her peripheral blood counts were normal and at autopsy she had no evidence of breast cancer.

Thus, the regimen of Bu 16 mg/kg and Cy 120 mg/kg is probably too toxic with at least 2/4 patients dying from regimen related toxicity. A similar phenomenon was observed in a group of patients receiving transplants for multiple myeloma. Among a group of 6 patients who received Bu 16 mg/kg and Cy 120 mg/kg, there were at least 3 early deaths from regimen related toxicity (2 VOD, 1 interstitial pneumonia). A subsequent group of 5 patients received Bu 14 mg/kg and Cy 120 mg/kg followed by allografting (4 patients) or autografting (1 patient). None of these patients experienced grade 3 or 4 regimen related toxicity. This would indicate that high dose Bu, when used in combination with high dose Cy, has a very steep dose toxicity curve