



## Alternating MOPP and ABVD Chemotherapy Plus Mantle-Field Radiation Therapy in Patients With Massive Mediastinal Hodgkin's Disease

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Seventy percent of patients with [Hodgkin's disease](#) have tumor involving the mediastinal nodes, which lie in the chest near the heart and great vessels. A subset of these patients have what is termed massive mediastinal disease which is defined one of two ways: 1. Lymphadenopathy measuring greater than one-third the greatest diameter of the chest or 2. Lymphadenopathy >35% of the chest diameter at thoracic vertebra number 6 on a chest radiograph.

Traditionally the treatment of massive mediastinal disease was with [radiation](#), but more than half the patients recurred after radiation, often at the edge of the treatment field. These results led to the current treatment recommendation of radiation and [chemotherapy](#) (called combined modality therapy). While combined modality therapy has improved disease-free survival rates, little impact has been seen on overall survival when compared to radiation alone.

Hodgkin's disease is often treated with combination chemotherapy regimens, which means that several chemotherapy drugs are given at the same time. Two often used regimens involve the use of four drugs: The MOPP regimen utilizes Mechlorethamine, Oncovin (vincristine), Procarbazine and Prednisone; the ABVD regimen uses Adriamycin, Bleomycin, Vinblastine and Decarbazine. Both of these regimens are dosed in 6 cycles over several months. The toxicity of these regimens includes potentially fatal pneumonitis with ABVD and the risk of leukemia and infertility with MOPP. The risk of toxicity is directly related to the amount of chemotherapy given and therefore investigators have looked to decrease the amount of drug dosed. One way to accomplish this without compromising cure is to use all eight drugs at a decreased dose for each, or to alternate the cycles, thereby gaining less cycles of each regimen.

Investigators at the [National Cancer Institute](#) undertook a prospective study in 1981 to determine the safety and efficacy of alternating MOPP and ABVD followed by radiation in patients with massive mediastinal Hodgkin's disease of any stage. Prior reports of this patient population focused on patients with stage I and II disease (that is, disease limited above the diaphragm). This report is the first to have a sizable number of patients with advanced disease. In addition, a novel treatment approach was devised: in an effort to reduce recurrence at the radiation field edge, the initial 10Gy of radiation was prescribed to the original extent of disease.

Eighty patients were enrolled in this study between 1981 and 1989. Thirty percent of the patients had advanced stage disease and almost all patients had nodular sclerosis type Hodgkin's disease. The radiation portals were simulated (i.e. set-up) prior to the start of chemotherapy even though radiation would start months later, to ensure that the original disease extent was covered for the initial 10Gy of radiation.

The vast majority of patients completed all six cycles of chemotherapy and were then treated with radiotherapy. Chemotherapy dose reductions were made as necessary according to published recommendations. The initial 10Gy was to the area of initial gross disease after which blocks were used to shape the radiation portals to areas of gross residual abnormality as seen on chest radiographs. Doses of 35-45Gy were used. Blocks to spare the spinal cord, heart and voice box were utilized.

Of the 80 enrolled patients, 90% achieved a complete remission following the chemoradiotherapy. Eight of 9 patients who failed to attain a complete remission died. The large majority of patients who obtained a complete remission remained free of disease at the time the study was reported. Approximately one-half of the patients that relapsed were successfully salvaged and remain free of disease. None of the prognostic factors examined exerted a significant impact on survival, including stage, age, platelet count, LDH level, sedimentation rate, sex, histology, B symptoms, and number of extranodal sites. Overall survival was worse for patients with advanced stage disease compared to early stage, 64% versus 79%, but this was not statistically significant.

Toxicity from chemotherapy and radiation was not insignificant. One patient died of treatment related pneumonitis- but it is noted that this was the oldest patient in the study (51y.o.) and she had a long smoking history and continued to smoke during therapy. Acute treatment morbidity was modest and few patients required admission to the hospital. 20% of patients developed pneumonitis requiring medication with steroids. The risk of pneumonitis was related to the total dose of radiation and occurred more commonly in patients receiving >40Gy.

Chronic treatment related toxicity has been reported in a number of study participants. Two-thirds of patients developed hypothyroidism requiring medication. Ten percent experienced pulmonary problems including infections and shortness of breath- although none are disabled for this reason. Six of the 61 surviving patients developed cardiac symptoms, but only one of the six had a significant decline in performance status secondary to cardiac problems. Of the 12 women in the study who desired children following treatment, all were able to conceive healthy children. However, only two of the six men who attempted to conceive were successful.

Three patients developed malignancies which were likely treatment related: One 19 year old women died of acute myeloid leukemia, a 42 year old developed two cancers following therapy - a parotid tumor and lung cancer and has been successfully treated for both- and a third women developed breast cancer. The true incidence if secondary malignancies cannot conclusively be stated because the risk for developing a second cancer continues into the third decade after treatment.

Although there is no prospective randomized trial comparing radiation alone versus chemoradiotherapy for early stage patients with massive mediastinal, the historical series show these two treatment strategies to offer similar survival rates. It is unclear if the strategy of radiation alone -which would allow approximately one half the patients to relapse- so as to avoid chemotherapy in the other half is advisable. Ideally, selecting patents who are at high risk for relapse and treating them with combined modality therapy is the goal, but good predictive assays remain elusive. In this series, none of the selected factors were prognostic on univariate analysis.

The authors conclude that combined modality therapy consisting of alternating 6 monthly cycles of MOPP/ABVD followed by mantle radiotherapy is a effective treatment for massive mediastinal Hodgkin's disease of any stage. Although the acute and chronic toxicity from this treatment is significant, the poor outcome with either therapy alone justifies the risks.

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