Randomized Study of Intensive MOPP-ABVD With or Without Low-Dose Total-Nodal Radiation Therapy in the Treatment of Stages IIB, IIIA2, IIIB, and IV Hodgkin's Disease in Pediatric Patients: A Pediatric Oncology Group Study

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Hodgkin's lymphoma or disease (HD) treatment has evolved tremendously over past several decades. The possibility of cure has become a reality for most patients diagnosed with this disease, despite even advanced disease. The standard of care for advanced HD has been combined modality therapy (CMT) with radiation and chemotherapy. The radiation utilized is usually low dose therapy to involved nodal regions, subtotal or total lymphoid or nodal irradiation (TNI).

Looking back at some of the previously reported HD experience by the Children's Hospital of Philadelphia, Joint Center for Radiation Oncology in Boston, Dana Farber Institute, Stanford, Princess Margaret Hospital in Canada, Germany, France, POG, Children's Cancer Study Group (CCSG) and others, success rates have been high. For earlier stage disease, radiation therapy (XRT) alone, full dose XRT combined with chemotherapy (CTX) and low dose XRT combined with CTX the overall survival rates (OS) have been 83 - 97%, 86 - 94% and 90 - 100%, respectively. Relapse free survivals (RFS) were 64 - 82%, 84 - 95% and 88 -96%. The distinction between low dose and full dose is an arbitrary one specified by the investigator, but as a general rule full dose is greater than 3000 - 4500 rads or centigray (cGy) and low doses are 1500 to 3000cGy. For advanced stage, as stated earlier, CMT has been the standard with chemotherapy regimens consisting of:

- Mechlorethamine/Vincristine/Procarbazine/Prednisone MOPP) Doxirubicin/Bleomycin/Vinblastine/Dacarbazine (ABVD)
- Ara-C/VP-16
- Cytoxan/Vincristine/Prednisone/Procarbazine (COPP)
- Vincristine/Prednisone/Procarbazine/Doxirubicin (OPPA)
- Vincristine/Etoposide/Prednisone/Doxirubicin (OEPA)

The radiation has been for the most part low dose (2000 - 3000cGy) to involved field or TNI. The earlier studies have shown an OS rate of 60 - 95% and RFS rate of 63 - 90%.

Success is not without its drawbacks. There have been studies demonstrating the toxicity of treatment for HD. Both CTX and XRT are major contributors, unfortunately. It has been demonstrated that over 3500cGy of XRT to growing bones in children leads to decreased growth and development of varying degrees. Less than 2500cGy of XRT is much less of a risk in growth suppression. Mantle field irradiation (XRT to the lymph node regions of the lower neck, upper chest, axilla, and mediastinum) occasionally leads to suppression of clavicular growth, female breast development, neck and upper chest muscle development. Pericardial fibrosis or effusions along with non-symptomatic left ventricular end diastolic volume decrease is seen infrequently in patients treated with Adriamycin (Doxirubicin) and XRT. Bleomycin and XRT has a tendency to increase the pulmonary fibrosis or pneumonitis that occurs after treatment. The rate of second malignancy is approximately

17.6% at 15years with CMT. It is difficult to fathom out whether the second malignancy is related just to the treatment or to the possibility that the patient is more genetically predisposed.

In recently published studies by the Eastern Cooperative Oncolgy Group (ECOG) and Southwest Oncolgy Group (SWOG), there were no significant differences in overall outcome in adult HD patients that did or did not receive radiation therapy after obtaining a complete response with chemotherapy. Based upon these compelling findings, POG set out to answer the question whether less treatment was better in regards to toxicity and still able to maintain the same cure rate.

MATERIALS AND METHODS:

One hundred and eighty-three patients were enrolled between November 1987 and February 1992 with stage IIB, IIIA2, IIIB, IV HD. They were randomized to receive either CTX plus XRT or CTX alone. Central pathology was utilized to review all biopsies. All patients received a chest x-ray, CT scan of the chest, abdomen and pelvis, gallium scan, bone scan, and bone marrow biopsy. Lymphangiogram was optional. Staging laparotomy with splenectomy was done if the patient was clinically staged as I, IIA or IIIA. Mini-lap (consisting of a wedge biopsy of the liver and multiple needle biopsies along with lymph node sampling) was done if: 1) spleen below left costal margin or two to three times normal size 2) filling defects in liver or spleen 3) greater than three cm lymph nodes on CT at the porta hepatis or splenic hilum.

The chemotherapy was an alternating regimen of MOPP and ABVD for a total of eight cycles in all patients. The first cycle would be MOPP followed a month later by a cycle of ABVD and then repeated. The radiation was either TNI or sub-TNI, given after a complete response (CR) to CTX. TNI treatment fields included a mantle, para-aortics, spleen and pelvic lymph node regions. Sub-TNI fields were used in patients with no HD below the aortic bifurcation and omitted the pelvic lymph node regions from the fields. These areas were treated to a total dose of 2100cGy in 150cGy/day fractions. The radiation was sequential, meaning that the mantle regions were treated first, then the spleen and para-aortics, and finally, the pelvic lymph node regions if necessary ? treatments were separated by two weeks. The patient was restaged after the third and sixth cycle of CTX, completion of CTX, and completion of XRT.

One hundred and seventy-nine were eligible for evaluation. After eight cycles of CTX, 161 (90%) patients had a CR. Eighty of those 161 patients were randomized already to receive XRT. For all patients, the event-free survival (EFS) and overall survival (OS) were 79% and 92% at five years, respectively. This is demonstrated in figure three. When comparing the two groups of XRT vs no XRT, the actuarial EFS rates at five years were 80% versus 79%, respectively. The five year OS rates were 87% versus 96% in favor of no XRT, but not statistically significant. Looking a several variables, age less than or equal to 13 years at diagnosis yielded a better prognosis. Similarly, those that had a clinical CR after the third cycle of CTX had a better prognosis (93% EFS) than those that took longer to obtain a CR. Toxicities seen were myelosuppression (48%), severe neutropenia (38%) of which two patients died of sepsis, and mild nonsymptomatic cardiopulmonary disease (four patients). Six second malignancies were seen - three patients with acute myelogenous leukemia (AML), one with nonhodgkins lymphoma (NHL), and another with malignant melanoma.

COMMENTS:

This study's importance is based firmly on the fact that it is the first randomized trial looking a the utility of adding XRT to HD after a CR. It seems to show that it is unnecessary to add post-CTX XRT. BUT before eliminating XRT from the treatment regimen, the date must be looked at further. It is noted that 10 of the 80 patients did not receive the XRT and were analyzed in the CMT group. Based on such a high number of noncompliance, it is difficult to fully interpret the data as XRT having no beneficial role. A further analysis of actual treatment may have been helpful. One must continue to individualize treatment to the patient and perhaps reserve XRT for those deemed at higher risk of relapse. The data on toxicity and second malignancies are in accordance with those seen previously in historical data. The incidence of AML is similar to previous reports, while follow-up is too short to know what the solid tumor rate will be. Finally, this is a study that will be widely quoted, but should be viewed cautiously with its notable shortcoming. The Childrens Cancer Group (CCG) is currently running a similar trial looking at all clinically staged HD for utility of XRT post CTX.