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Treatment approaches in early stage Hodgkin's lymphoma

Introduction

Combined modality treatment (CMT) with radiation therapy (RT) and chemotherapy has largely replaced RT alone for the treatment of early stage Hodgkin lymphoma.[1-3] A major concern remains the late toxicities of treatment most of which are attributable to the RT, although recent CMT regimens have reduced the size of the RT portals and the doses of RT in an attempt to reduce toxicity. Recently several studies have suggested that chemotherapy alone is a reasonable treatment option for patients with early stage non-bulky Hodgkin lymphoma. Combined modality treatment remains the standard treatment for early stage HL with bulky disease (mediastinal mass >1/3rd the thoracic diameter or peripheral nodal mass >10 cm), since RT to regions of tumor bulk in combination with chemotherapy has been demonstrated to reduce the risk of recurrence.[4,5] Positron emission tomography (PET) may eventually define a subgroup of patients with early stage bulky disease who can be followed without additional RT after chemotherapy.[6]

Long-term toxicity of treatment

The risks of sterility and secondary leukemias and myelodysplastic syndromes have been decreased with the current standard ABVD (doxorubicin, bleomycin vinblastine, dacarbazine) chemotherapy regimen as compared with alkylating chemotherapy regimens of the MOPP (nitrogen mustard, vincristine, procarbazine, prednisone) type.[7,8] Most of the late complications of treatment seen in Hodgkin lymphoma survivors are related to radiation therapy. The rate of second malignancies is approximately 1% per year so the incidence of second malignancies is approximately 25-30% at 25-30 years following successful treatment.[9,10] Among solid tumors, only alkylating agent-based regimens are associated with an increased risk of lung cancer.[11] Second malignancies are the leading cause of late morbidity and mortality.[12,13]

Cardiovascular damage is the second most frequent cause of late mortality and morbidity.[12,13] Carotid stenosis risk is increased after cervical RT, and the relative risk of stroke is increased 5-6 times after mantle RT.[14] Patients who receive mantle field RT have a 2-7 times increased risk of fatal myocardial infarction.[15] Heart valve fibrosis requiring surgical replacement,[14] and more subtle abnormalities such as restrictive cardiomyopathy and conduction abnormalities have also been

reported following mediastinal RT.[16] Neck muscle wasting causing difficulty with neck extension is common following RT to the neck and may cause discomfort. Pulmonary and pericardial fibrosis and brachial plexopathies due to fibrosis are less common late complications of RT.

Secondary hypothyroidism is usually manageable with thyroid replacement therapy.

Chemotherapy alone in the treatment of non-bulky early stages of Hodgkin's lymphoma

Three randomized trials comparing chemotherapy alone to chemotherapy and radiation therapy have been reported recently. To determine whether CMT is superior to chemotherapy alone, 152 untreated Hodgkin's lymphoma patients with CS IA, IB, IIA, IIB, and IIIA without bulk disease treated at Memorial Sloan-Kettering Cancer Center (MSKCC) were prospectively randomized to 6 cycles of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) alone or 6 cycles of ABVD followed by RT (3600 cGy: involved field for 11 patients, modified extended field for the rest). Sixty-five of 76 patients randomized to receive RT actually received it and 11 did not (4 progressed, 1 bleomycin toxicity, 6 refused). For ABVD+RT, the complete remission (CR) percentage was 94% and no major response 6%. For ABVD alone, 94% achieved a CR, 1.5 % a partial response (PR) and no major response 4.5%. At 60 months CR duration, freedom from progression (FFP), and overall survival (OS) for ABVD$^+$ RT *vs.* ABVD alone are 91% *vs.* 87% (p=0.61), 86% vs. 81% (p=0.61) and 97% *vs.* 90% (p=0.08), respectively (logrank). The 95% confidence intervals for CR duration, FFP and OS differences at 5 years were (-8%, 15%), (-8%, 18%) and (-4%, 12%), respectively. Although significant differences were not seen, it is possible that a benefit in outcome of <20% for CMT might be seen in a larger trial.[17]

A non-randomized study from Spain demonstrated progression-free survival of 87% and an overall survival of 97% at 78 months in 80 patients with non-bulky stages I and II Hodgkin's disease treated with six cycles of ABVD alone, results similar to the MSKCC experience.[18] The results of a randomized phase II trial conducted by the National Cancer Institute of Canada (NCIC) and the Eastern Cooperative Oncology Group was recently reported.[19] In this trial, patients with CS IA and IIA Hodgkin lymphoma without tumor bulk or other poor prognosis features were randomized to "standard" treatment (subtotal lymphoid irradiation [STLI]) for more favorable; 2 cycles of ABVD + STLI for less favorable or "experimental" treatment (4-6 cycles of ABVD alone). On the "experimental" arm, 29% of patients received only 4 cycles of ABVD, although it is not clear that excessive relapses were seen in this subgroup. At a median duration of follow-up of 4.2 years, the estimated 5-year progression-free survival was 93% for patients in the "standard" arm and 87% for those in the "experimental" arm, a difference that was statistically significant. There was no difference in event-free or overall survival. In view of the salvageability of the small excess for patients who might relapse after chemotherapy alone and the late morbidity of treatment that is mostly attributable to RT, the clinical meaning of a 6% difference in PFS is unclear. Also, it is quite possible that events will continue to occur in the combined modality arm with time due to late effects of RT. Six cycles of ABVD alone has been more commonly used for Hodgkin's disease patients than 4 cycles for which this is the first reported experience. It is possible that four cycles of ABVD without RT is less adequate chemotherapy than the more standard 6 cycles. Also, nei-

ther STLI nor 2 cycles of ABVD + STLI are currently the most commonly used "standard" treatments for early stage Hodgkin lymphoma. Thus the results of this trial are not conclusive.

Preliminary results of the EORTC-GELA H9-F trial were recently reported.[20] This trial randomized early stage patients with Hodgkin lymphoma and favorable features to chemotherapy alone with epirubicin, bleomycin vinblastine and prednisone (EBVP), EBVP and 20 Gy involved field radiation therapy (IF RT) or EBVP and 36 Gy IF RT. The four-year event-free survival was 69% for EBVP alone versus 85% for EBVP and 20 Gy IF RT and 88% for EBVP and 36 Gy IF RT ($p<0.001$). The EBVP only arm was discontinued because of this difference. There was no difference in overall survival in the three arms of the trial. A potential flaw of this trial is that EBVP may be inferior to standard chemotherapy. In their H7-U trial for early stage patients with unfavorable features, EBVP and IF RT was inferior to the more standard MOPP/ABV hybrid and IFRT.[21]

Pulmonary toxicity with doxorubicin, bleomycin vinblastine, dacarbazine

Pulmonary toxicity from bleomycin treatment is a problem with the ABVD regimen. The major non-hematologic toxicity is pulmonary and related to bleomycin. In the trial conducted at MSKCC, 33 patients (22%) discontinued bleomycin because of a decrease in DLCO. Ten of the symptomatic patients received brief courses of corticosteroids, and there was one death due to bleomycin during treatment in a 65-year-old woman.[17,22] Similar findings were recently reported by Bonadonna and colleagues.[22] Bleomycin pulmonary toxicity was associated with a significant decrease in 5-year overall survival in patients with Hodgkin lymphoma and the overall mortality rate was 4.2% in a recent retrospective report from the Mayo Clinic.[23]

Triplet chemotherapy without bleomycin

Gemcitabine is one of the most active single agents for relapsed Hodgkin lymphoma with response rates of 39-43% and less pulmonary toxicity than bleomycin.[24,25] Promising results were reported in relapsed and refractory Hodgkin lymphoma patients with the combination of gemcitabine, vinorelbine, and liposomal doxorubicin in CALGB 59804.[26] For these reasons CALGB conducted a phase II trial of gemcitabine, vinblastine and doxorubicin (AVG) as initial treatment for patients with non-bulky stages I and II Hodgkin lymphoma (CALGB 50203).[27] Although the populations of patients treated had several adverse prognostic features including advanced age and multiple sites of involvement, the results were somewhat disappointing. The CR + CRu rate was 67.7% with one-year progression-free survival of 78%. Although this was not a randomized trial formally comparing AVG to a more standard regimen such as ABVD, this regimen is not being pursued in future trials.

Dacarbazine which is an alkylating agent, but not of the nitrogen mustard class was initially selected for the ABVD regimen based on a single small phase II report. However, it may be an important component of combination chemotherapy for Hodgkin's lymphoma. Several reports have demonstrated that patients on ABVD who must have bleomycin discontinued because of toxicity can be continued on AVD with omission of bleomycin and have a similar outcome to patients who receive a full course of ABVD.[17,23,28] Promising results are being seen with 2 cycles of AVD and involved field RT in favorable early stage Hodgkin's lymphoma in the HD13 trial[29] of the German Hodgkin Study Group.

Prognostic significance of PET scans performed during treatment and after treatment

[18F]FDG PET scanning has been found to be useful in predicting recurrences in residual masses following treatment for Hodgkin's disease. False negative studies are less common (negative predictive value 95%) than false positives (positive predictive value 60%).[30]

In British Columbia, patients with patients with advanced stage or early stage with tumor bulk had CT scans performed after 6 cycles of ABVD. Those with residual masses ≥2.5 cm had PET CT scans performed. Patients who were PET+ received additional consolidative RT and those who were PET- were followed. Although there was a significantly lower 2-year disease-free survival for patients who were PET^+ as compared to those who were PET^-, there was no difference in 2-year disease-free survival between patients with or without initial bulky disease who were PET^-. Although consolidative RT remains standard for patients with initial bulky disease, if confirmed, these results suggest that PET/CT scans may identify a subpopulation of these patients who will not require RT6.

The studies of Kostakoglu,[31] Hutchings[32,33] and Gallamini[34] have demonstrated that progression-free survivals are inferior for patients who are PET^+ during chemotherapy after 1 or 2 cycles of treatment. Several groups including CALGB and SWOG in the U.S. are designing trials to look at intensification of treatment for those patients who are PET^+ after the first few cycles of standard treatment.

Conclusion

A number of recent clinical trials for the treatment of early stage Hodgkin lymphoma have attempted to reduce long-term toxicity with the elimination of RT when it is not necessary. The role of functional imaging with PET during treatment to tailor treatment is under investigation in current clinical trials.

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