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Current directions in the treatment of early stage Hodgkin's lymphoma

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Radiation therapy (RT) alone and the combined modalities therapies (CMT) of chemotherapy and RT for early stage Hodgkin lymphoma have achieved excellent results for early stage Hodgkin lymphoma for over thirty years. A major concern has been the late toxicities of treatment most of which are attributable to the RT. Recently several studies have suggested that chemotherapy alone is a reasonable treatment option for patients with early stage non-bulky Hodgkin lymphoma. At the present time this does not seem to be appropriate for patients with early stage 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.

Long-term toxicity of treatment

Most long-term toxicity of chemotherapy for Hodgkin lymphoma seems to be related to alkylating agent and procarbazine-containing regimens of the MOPP type. The complications of infertility in most men and in women, particularly over the age of 30 years and the approximately 3% lifetime risk of acute leukemia have long been recognized.[1] Among solid tumors, only alkylating agent-based regimens are associated with an increased risk of lung cancer.

Vascular damage to coronary and peripheral arteries is a concern with RT. Carotid stenosis risk is increased after cervical RT.[2] Patients who receive mantle field RT have a three-fold increase risk of fatal myocardial infarction.[3] Heart valve fibrosis requiring surgical replacement,[2] and more subtle abnormalities such as restrictive cardiomyopathy and conduction abnormalities have also been reported following mediastinal RT.[4] The actuarial risk of second malignancies is 22-27% at 25-30 years[5-9] following treatment for Hodgkin's disease. As mentioned above most of this risk seems to be related to RT.

Neuromuscular problems are another late complication related to RT. Neck muscle atrophy resulting in neck pain and difficulty in neck extension occurs in some patients.[10] Symptomatic radiation pulmonary and pericardial fibrosis and brachial plexopathies occur but less frequently than in the past with current RT techniques.[11-13] Secondary hypothyroidism is usually manageable with thyroid replacement therapy.

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

Three randomized trials comparing chemotherapy alone to chemotherapy and radiation therapy have been reported recently. To determine whether combined modality therapy (CMT) is superior to chemotherapy alone (CT), 152 untreated Hodgkin 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.[14]

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.[15]

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 reported16. 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, neither 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.[17] 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.[18]

Pulmonary toxicity with ABVD

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.[14,19] Similar findings were recently reported by Bonadonna and colleagues19. 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.[20]

Gemcitabine

Gemcitabine is a highly effective and potentially less toxic drug than bleomycin for the treatment of Hodgkin lymphoma. The overall major response rate in refractory Hodgkin lymphoma is approximately 40%.[21,22] Recently experience with gemcitabine in combination with doxorubicin and vinca alkaloids in patients with Hodgkin lymphoma has been reported. Bartlett and colleagues described the preliminary results of CALGB 59804, a phase I/II study of gemcitabine, vinorelbine and pegylated liposomal doxorubicin[23] (Doxil®) in relapsed Hodgkin lymphoma). For patients who had not received prior stem cell transplants, the phase II doses were gemcitabine 1000 mg/m^2 on day 1 and day 8; vinorelbine 20 mg/m^2 on day 1 and day 8; and pegylated liposomal doxorubicin 15 mg/m^2 on day 1 and day 8 administered every 21 days. In 47 patients with relapsed Hodgkin lymphoma without prior transplant, the overall response rate was 66% with 19% CR and 47% PR. Grade 3/4 neutropenia was seen in 59% of patients in the phase II trial. There were no treatment related deaths.

Mild reversible dyspnea, often not requiring cessation of drug, has been reported overall in approximately 25% of patients treated with gemcitabine. Severe pulmonary toxicity has been reported in less than 1% of patients (data supplied by Eli Lilly and Company). The combination of gemcitabine with chemotherapy including bleomycin for the treatment of Hodgkin lymphoma has caused unacceptable pulmonary toxicity.[24,25] The use of gemcitabine with doxorubicin and vinca alkaloids appears to be effective and safe as long as the drugs are not combined with bleomycin.

AVG

A new trial has been initiated for patients with non-bulky stages I and II Hodgkin lymphoma (CALGB 50203). It employs doxorubicin, vinblastine and gem-

citabine (AVG), a new combination of 3 of the most active chemotherapeutic drugs in the treatment of Hodgkin lymphoma. It follows up on the excellent results with pegylated liposomal doxorubicin (Doxil®), vinorelbine and gemcitabine in relapsed Hodgkin lymphoma (CALGB 59804). Radiation therapy has been omitted based on the results at MSKCC results with ABVD chemotherapy alone, the potential long-term morbidity of radiation therapy and likelihood of successful salvage of patients with persistent or relapsed disease in this population following chemotherapy only. As with the MSKCC trial, 6 monthly cycles of chemotherapy are administered on days 1 and 15 of each cycle (12 treatments). It eliminates bleomycin, the drug with the most problematic toxicity.

A novel aspect of this trial is the prospective use of positron emission tomography (PET) imaging in assessing responses to treatment in Hodgkin lymphoma, early on (after two cycles of chemotherapy) and at the completion of treatment (after 6 cycles of treatment). Recently, PET imaging after 1 or 2 cycles of chemotherapy has been found to be highly predictive of out come.[26-28]

Conclusions

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 and to devise less acutely toxic chemotherapy regimens. The role of functional imaging with PET in assessing response and predicting outcome is also being explored prospectively.

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