HODGKIN'S LYMPHOMA

Treatment options in early stages of Hodgkin’s Lymphoma, high cure rate with lower short and long-term toxicity

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Abstract
The definition of early stages in HL varied among cooperative groups and clinical trials. Most of them considered early stages: stage I, II, and IIIA without bulky disease. Bulky disease has been defined at the Costwolds Meeting as those tumors with more than 10 cm or a mediastinal involvement of more than one-third of the chest wall diameter. Other factors that have been considered unfavorable within the early stages are old age, high ESR, mixed cellularity or lymphocyte depleted histology, B symptoms or multiple sites of disease.

Keywords: Hodgkin’s lymphoma, early stage, treatment

Brief history of the therapy of HL from 1960s to 1980s
The standard treatment in pathological stage I–II HL in 1960s and 1970s was total nodal irradiation (mantle and inverted Y) at 35 Gy to 40 Gy. The combination of chemotherapy MOPP and MOPP like regimens (COPP, CVPP, LOPP, etc.) were used in the 1970s only in advanced stages or in patients relapsing to radiotherapy. ABVD emerged as a second-line treatment in patients who relapsed or were refractory to MOPP. In the 1980s MOPP was used with ABVD as sequential, alternated or hybrid form in order to increase response rate and DFS.

Best combination chemotherapy
Randomized studies done by European and later by USA groups demonstrated better results with ABVD than MOPP, and similar results with ABVD versus alternated or hybrid MOPP/ABVD with less myelosupression, gonadal toxicity and second malignancies. The German Hodgkin’s Disease Study Group (GHSG) performed the HD11 trial in 1047 intermediate stage patients. It showed that there was no difference for the comparison between four courses of ABVD and four courses of standard BEACOPP, or for the comparison of 20 Gy IFRT with 30 Gy IFRT, with a 90% DFS rate and 97% OS rate at 2 years [1].

The EORTC and GELA randomized 808 patients in the H9-U trial in stage I–II with unfavorable clinical features to 6 vs. 4 cycles of ABVD vs. 4 cycles of BEACOPP baseline followed by 30 Gy IFRT in all the arms. The 4 years DFS were 94%, 89%, and 91% in the 3 arms respectively ($P=0.23$). The 4 years OS rates were 96%, 89%, and 93% respectively ($P=0.89$) [2].

Number of cycles of chemotherapy
The GATLA performed a randomized study in stage I–II without bulky disease of CVPP for 3 vs. 6 cycles without radiotherapy. The DFS at 5 and 10 years were 85% and 85% for these treated with 3 cycles; 93 and 73% for 6 cycles of CVPP. The OS at 10 years were 89% in both arms concluding that 3 cycles of CVPP without radiotherapy were equally effective than six cycles [3].

The GHSG in a trial HD 10 compared in stage I–II without risk factors 4 vs. 2 cycles of ABVD and 30 Gy vs 20 Gy of IFRT. The DFS and OS at 2 years in 847 evaluable patients was 97% and 98% respectively,
with no statistical difference between ABVD 2 vs. 4, and IFRT 30 Gy vs. 20 Gy [4].

**Extended field vs. involved field radiotherapy as consolidation after chemotherapy**

The GHSG randomized 1064 patients with early stage unfavorable prognosis after 4 cycles of alternate COPP and ABVD to extended-field radiotherapy or IFRT 30 Gy plus 10 Gy to bulky disease. The CR, DFS and OS were 98%, 83% and 91% at 5 years without difference between type of RT arms [5]. Bonadonna et al. [6] showed that in 136 patients with early stage of HL after 4 cycles of ABVD, 36 Gy of subtotal nodal plus spleen irradiation were equivalent to IFRT. The overall 12 years DFS and OS were 93% and 95% respectively.

**Chemotherapy vs. combined modality therapy**

The Canada Clinical Trial Group (CCTG) and the Eastern Cooperative Oncology Group (ECOG) reported the results of a randomized trial comparing ABVD 4–6 cycles alone vs. ABVD plus STNRT 35 Gy in limited-stage HL. No difference was observed in DFS (88% vs. 86%), or OS (94% vs. 96%) between both treatment modalities [7].

Strauss et al. [8] randomized 152 untreated stage I–IIIA nonbulky HL to 6 cycles of ABVD alone versus ABVD followed by 36 Gy of radiation. The 5 years DFS and OS for ABVD and ABVD + RT was 81% vs. 86% and 90% vs. 97% being the differences not significant.

In the current trial of the Argentine Group for Treatment of Acute Leukemia (GATLA), patients with stage I–IIIA without bulky disease and who achieved CR after the third cycle of ABVD received IFRT 25 Gy. A total of 172 patients were evaluable, the DFS and OS at 60 months were 92% and 98% respectively [9].

The GHSG compared in a trial, patients who received eight cycles of BEACOPP, 30 Gy IFRT or no radiation to bulk or residual disease. CR was achieved in 93%, the DFS for the total group was 89% and OS was 95%. There was no difference for DFS or OS in an attempt to treat analysis between the RT and no RT arm [10].

The GATLA has compared 6 cycles of CVPP vs. 6 cycles of CVPP plus IFRT 30 Gy in early stages of HL without bulky disease. Also, the comparison of the DFS and OS at 5 and 10 years showed no difference (3).

The EORTC and GELA (2) in a H9-F trial compared in 783 patients with early and favorable disease who achieved CR after 6 cycles of EBVP, 36 Gy vs. 20 Gy of IFRT vs. no radiotherapy. The 4 years DFS was 87%, 84% and 70% respectively ($P < 0.001$) being superior in the two arms with radiotherapy.

**Second malignancies**

The combination of regimens that included alkylating agents as MOPP, BEACOPP, has shown to produce higher rate of AML/MDS, mainly during the first 5 years since treatment started. The incidence of second solid tumor continued to increase compared to the normal population more than 30 years later. However most of the long-term reports were in patients treated two or three decades ago with MOPP like regimens and wider fields and higher doses of radiation, that is not the current practice today.

**Conclusion**

The current treatment of choice for localized stages without “bulky” disease is 2 or 4 cycles of combined treatment with ABVD and low doses of radiotherapy (20 to 25 Gy) to involved areas in partial responders or bulky disease at diagnosis. The new imaging techniques as positron emission tomography (PET) will help more sensitive discriminate between early responders, late responders, and nonresponders with ABVD chemotherapy and tailored consolidation radiation therapy only for these late responders, and nonresponders that probably will be less than 20% of the early stages of HL.

**References**


