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Management of advanced Hodgkin's lymphoma

G.P. Canellos

Dana-Farber Cancer Institute, Boston, Massachusetts, USA

The relative safety of ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) and its demonstrated equivalence or superiority to MOPP (nitrogen mustard, vincristine, procarbazine, prednisone) or MOPP-containing regimens, including hybrid regimens, in prospective trials led to its widespread use as the standard regimen for the treatment of Hodgkin lymphoma.[1] The ABVD regimen is shown in Table I. In all instances, the patients treated with MOPP or its variants had the known higher rates of septic complications due to the greater degree of myelosuppression as well as an increased likelihood of developing myelodysplasia or acute leukemia compared to ABVD. The ABVD regimen did not appear to have permanent sterilization as a toxic effect. It did, however, entail degrees of pulmonary compromise secondary to bleomycin that, in the majority of patients, was demonstrated by radiographic or clinical changes. It was reversible by cessation of bleomycin and, in some instances, requiring corticosteroids.[2] Discontinuation of the bleomycin component of ABVD in such patients does not compromise the outcome compared to patients who complete a full course of chemotherapy.[3] There is a reasonable doubt as to the essential contribution of bleomycin in the ABVD regimen. Other regimens, without classic alkylating agents such as EVA or AV, VEEP or NOVP (outlined in Table 1), have activity also without bleomycin.[4-7]

The impact of ABVD in most series with advanced disease resulted in 60-70% of patients achieving a durable complete remission (CR). Failure or relapse from CR will occur in 30-35%, and can be correlated with the presence of unfavorable clinical prognostic features.

At the time of this writing, there are a number of unknowns concerning ABVD. It is unclear whether 6 or 8 cycles are needed. In the past, it was usually recommended to give two cycles beyond complete clinical remission especially in the MOPP era. That decision was introduced before the general use of computerized axial tomography (CAT scans) with their greater accuracy and also the higher detection of a *residual* mass. It is anticipated that PET scans (positron emission tomography) will be useful in the assessment of residual disease still present on the CAT scan or routine radiograph. The current assessment of patients regarding *completeness* of remission includes radionuclide scans, gallium-SPECT or PET, usually 2-3 weeks following completion of 6 or 8 cycles of chemotherapy. PET scans following therapy of Hodgkin lymphoma have shown that a significant fraction of patients will show some faint residual or low intensity uptake. A fraction (~40%) will eventually revert to negative in follow-up and not relapse.[8] It is advisable, in that circumstance, to repeat the PET scan in 4-6 weeks as long as there is no clinical progression by clinical or routine radiographic evaluation.

Newer regimens

The fact that 30-35% of patients with advanced disease will relapse or fail to enter complete remission with ABVD has prompted further efforts to intensify the chemotherapy and thereby hopefully improve the CR rate and ultimately the overall survival. The results of these newer programs are encouraging and are currently in randomized comparative trials with ABVD.

The first approach, as introduced by the Stanford University group as the Stanford V regimen, was compacting the chemotherapy within 12 weeks with different agents given on a weekly basis to increase the duration of drug exposure.[9] PACEBOM and VAPEC-B, which are similar to the Stanford V regimen, have been studied in the UK.[10,11] All of the above included radiation therapy to sites of original bulk or *residual* disease. (See Table 2) A randomized trial presented by one of the Italian cooperative groups suggested that Stanford V, as given by them, was not as effective in FFS in their hands as ABVD.[12] It should be noted that

Table 1. Non-alkylating combination chemotherapy regimens.

Regimen	*Dose (mg/m²)*	*Schedule (days)*
ABVD		
Doxorubicin	25 IV	1,15
Bleomycin	10 units	1,15
Vinblastine	6	1,15
Dacarbazine	375	1,15
EVA		
Etoposide	100	1,2,3
Vinblastine	6	1
Doxorubicin	50	1 q. 28 days
AV		
Doxorubicin	25	1,15
Vinblastine	6 q. 28 days	1,15
VEEP		
Vincristine	1.4 (2.0)	1,8
Epirubicin	50	1 q. 21 days
Etoposide	100	1-4
Prednisolone	100 PO	1-8
NOVP		
Mitoxantrone	10	1
Vincristine	1.4	8 q. 21 days
Vinblastine	6	1
Prednisone	100 PO	1-5

IV = intravenous; q = every; PO = orally.

the Stanford University results with Stanford V were exceptionally good, with freedom from progression at five years of 89% and 96% overall survival.[13] If avoidance of radiotherapy is a goal, then all of these regimens need to be compared to a standard with radiation therapy or preferably without radiation to assess their basic cytotoxic impact. There is currently a North American Intergroup trial comparing Stanford V/Radiation therapy to ABVD with optional radiation therapy. The pilot trial in the Eastern Cooperative Oncology Group in 47 patients was very positive with estimated freedom from progression of 85% at five years.[14] After completion of 12 weeks of chemotherapy, patients receive radiation therapy to sites that were 5cm or greater. This resulted in a majority having to receive radiation therapy. The degree of immunosuppression in Stanford V required continuous oral cotrimoxazole and acyclovir. These excellent results entailed about 20% of patients requiring hospitalization. The amount of nitrogen mustard appears to be minimal enough (3 injections) to avoid sterilization and secondary myelodysplasia. It is actually unknown whether the Stanford V or PACEBOM could stand alone as a systemic therapy without radiation therapy.

The second approach to increase the CR rate and survival is an intensification of the doses of chemotherapy and this was introduced by the German Hodgkin Disease Study Group.[15] The BEACOPP regimen (outlined on Table 2) has been given as *standard* or escalated regimen.[16] In escalated doses, it showed a statistical superiority in survival to their standard (COPP alternated with ABVD x 4) in a large prospective randomized trial with 1,200 patients.[17] The *standard* dose BEACOPP, although more active than COPP/ABVD in failure-free survival at five years, did not achieve a superior survival. Myelosuppression was significantly higher with the escalated dosage. In addition, the actuarial risk of secondary myelodysplasia/leukemia was 2.5% at five years analogous to that seen previously with MOPP. This same randomized trial also included radiation therapy to sites of prior disease > 5cm or convincing residual disease. Current trials have modified the program to 4 cycles of escalated BEACOPP and four cycles of standard dose, BEACOPP, to attempt to diminish the toxicity. This regimen has been shown to be comparable to 8 cycles of escalated BEACOPP in early analysis. Also, the addition of radiation therapy in this GHSG trial (HD12) did not show any early advantage.[18] A certain caution is required with dose escalation since this trial had a 3.3% mortality due to toxicity and AML/MDS continues to be seen.

Table 2. Hodgkin's lymphoma regimens delivered weekly over 3 months only (radiation therapy included).

Regimen	*Dose*	*Route (mg/m^2)*	*Schedule (cycle length/days)*
Stanford V			
Mechlorethamine	6	IV	wks 1,5,9
Adriamycin (doxorubicin)	25	IV	wks 1,3,5,9,11
Vinblastine	6	IV	wks 1,3,5,9,11
Vincristine	1.4	IV	wks 2,4,6,8,10,12
Bleomycin	5	V	wks 2,4,6,8,10,12
Etoposide	60 x 2	IV	wks 3,7,11
Prednisone	40	PO	wks 1-10 q.o.d.
G-CSF			Dose reduction or delay
BEACOPP (escalated BEACOPP)			28
Bleomycin	10	IV	8
Etoposide	100 (200)	IV	1-3
Adriamycin (doxorubicin)	25	IV	1
Cyclophosphamide	650 (1250)	IV	1
Oncovin (vincristine)	*1.4**	*IV*	*8*
Procarbazine	*100*	*PO*	*1-7*
Prednisone	*40*	*PO*	*1-14*
G-CSF	*-(+)*	*SQ*	*8+*

Patients presenting with poor prognostic features clearly need a more effective program than ABVD. Fortunately such patients represent no more than 15% but with a higher rate of relapse (40-60%) with *standard* regimens. Whether a significant improvement can be achieved with regimens like BEACOPP is the subject of the current international prospective trial comparing 4/4 BEACOPP to ABVD without radiation therapy in both arms of the trial.

Combined modality therapy for advanced disease: does it improve survival?

The value of complementary radiotherapy in advanced HD after achieving a CR or CR undetermined (CRu), partial response but with a negative PET scan has been questioned. Randomized trials and an extensive meta-analysis have suggested that overall survival is not significantly improved by adding radiation therapy to patients effectively treated with chemotherapy. The meta-analysis featured trials in which radiation was given concurrently or sequentially and in no subgroups was survival improved.[19] Randomized trials which compared the addition of radiation therapy after achieving complete remission to two additional cycles of chemotherapy showed no difference in survival outcome.[20,21] The EORTC (European Organization for Research and Development of Cancer) has completed a trial testing whether radiation therapy to prior sites of disease adds to the survival of patients with advanced disease who achieved a complete response. It did not improve the survival achieved with chemotherapy alone. Patients in partial response were irradiated and did as well as the CR patients.[22] These patients were not assessed with radionuclide scans. It is possible that some *PR* patients may have been *CR* with a residual CAT scan abnormality that may have been rendered free of tumor. Ten years previously, the Southwest Oncology Group (SWOG) trial of radiation following a CR achieved by MOP-BAP showed no impact on survival by the combined modality arm of the trial.[23]

Up until recently, radiation therapy was routinely given to *bulky* or prior sites of disease after a full course of chemotherapy. After the above-mentioned results, it would appear that patients in CR could be spared radiation if a CR or CRu is confirmed with a negative PET scan. The issue is not insignificant since the actuarial risk of radiation-induced secondary solid tumors and serious cardiovascular disease approaches 20-30% at 20-25 years of follow-up.[24-27]

Advanced nodular lymphocyte predominant Hodgkin's lymphoma (NLPHD)

The very low-grade nature calls into question whether cell-cycle active agents, such as doxorubicin, can achieve the same long-term benefits seen in classic HL. There are virtually no comparative studies of chemotherapy alone for NLPHD and thus ABVD continues to be used. There is a small series of salvage chemotherapy with ABVD for patients relapsing from radiation which showed a poor outcome with only 2/6 achieving durable responses as opposed to durable 8/12 treated with MOPP or MOPP-like regimens.[28] The CD20 positivity of NLPHD and rarely in classic HL may

contribute to the utility of the anti-CD20 antibody rituximab in patients requiring systemic therapy. Two published series showed a very high response rate in previously treated NLPHD patients of 100% and 86% respectively, including CR in 41% and 57%.[29, 30] The responses last a median of 10-20 months. Conversion to large cell lymphoma (LCL) can occur as a result of clonal progression in 3-7% of patients.[31]

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