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Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone outside German Hodgkin Study Group: the Italian experience

Hodgkin lymphoma (HL) is one of the most treatable adult cancers, with long-term cure rates of more than 80% achieved even in patients with advanced disease.[1,2] The combination of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD), is currently considered to be the standard treatment for HL worldwide.[3] As an improvement on the ABVD combination, other regimens, including Stanford V, MOPPEB-VCAD, EVA, VEBEP, and ChlVPP/ABVVP, have been proposed but none have so far been demonstrated to be more effective than ABVD.[4-9] In 1990, the German Hodgkin Study Group (GHSG) developed a dose-escalated and accelerated combined modality regimen consisting of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP), plus radiation therapy (RT). The HD9 trial compared cyclophosphamide, vincristine, procarbazine, and prednisone, plus doxorubicin, bleomycin, vinblastine, dacarbazine (COPP/ABVD) with both standard BEACOPP and escalated BEACOPP. This trial demonstrated the superiority of escalated BEACOPP, both in terms of failure free survival (FFS) and overall survival (OS).[10] Concern about the toxicity of BEACOPP has been raised, however, and further trials designed to identify a therapy with the best risk-to-benefit ratio have been initiated by several Cooperative Groups. One trial by the European Organization for Research and Treatment of Cancer (EORTC) is currently recruiting and randomizes patients with advanced HL between 4 escalated plus 4 standard courses of BEACOPP versus 8 courses of ABVD.

To date, two trials have been completed in Italy and their results recently disclosed. These trials were conducted independently by Gruppo Italiano per lo Studio dei Linfomi (GISL) (HD2000 study[11]), and by Fondazione Michelangelo (FM), Gruppo Italiano Terapie Innovative nei Linfomi (GITIL) and Intergruppo Italiano Linfomi (IIL).[12] In both cases, patients with advanced HL with slight differences were enrolled. In the GISL trial a third arm was included, consisting of an alternating hybrid regimen developed by the same group (COPPEBVCAD, CEC: cyclophosphamide, lomustine, vindesine, melphalan, prednisone, epidoxirubicin, vincristine, procarbazine, vinblastine, and bleomycin).[5,6] In the FM-GITIL-IIL trial the use of a high-dose salvage was considered as a preplanned treatment for both arms.

In the GISL trial, patients were randomly assigned to receive 6 courses of ABVD, 4 escalated plus 2 standard courses of BEACOPP, or 6 courses of CEC, and randomization was stratified by stage (IIB *vs.* III *vs.* IV). In the FM-GITIL-IIL trial patients were stratified and randomized to receive 6-8 courses of ABVD or 4 courses of escalated plus 4 courses of standard BEACOPP. The adoption of a less intensive BEACOPP schedule was shared by the two Italian trials and also by the ongoing EORTC trial, due to concerns regarding the safety profile associated with 8 full courses of escalated BEACOPP. RT was allowed in both trials and delivered to sites of initial bulky disease or residual masses.

Both Italian trials commenced in 2000 and were closed in 2007. The GISL study enrolled 307 patients, with 103, 102, and 102 allocated to the ABVD, BEACOPP, and CEC treatment arms, respectively. A total of 321 patients were enrolled in the FM-GITIL-IIL trial, 166 patients in the ABVD and 155 in the BEACOPP arm. The baseline characteristics of patients randomized in both trials are presented in Table 1. Overall, the response rates are similar in both trials, with CR rates of 84% and 77% for ABVD and 91% and 85% for BEACOPP in the GISL and FM-GITIL-IIL trials, respectively. After a median follow-up of 41 months for the GISL trial and 30 months for the FM-GITIL-IIL trial, both trials showed comparable survival data. The estimated 5-year FFS, progression free survival (PFS) and OS rates of the two trials are summarized in Table 2. Patients randomized to BEACOPP had a better PFS than those allocated to ABVD. The PFS increased by 13% and 16% in the GISL and FM-GITIL-IIL trial, respectively. No differences were found in terms of OS. Additional multivariate analysis was performed for the HD2000 study to analyze the role of confounding factors. The better results obtained with BEACOPP in terms of the FFS did not change when the therapy was adjusted by the international prognostic score (IPS ≥3 *vs.* 0-2). A PFS analysis adjusted for IPS showed a HR of 0.46 (95% CI, 0.24-0.88) associated with BEACOPP, with a risk reduction in progression of 54% in comparison with ABVD. The magnitude of the improved results for BEACOPP over ABVD was more evident in patients with a high IPS (IPS 3-7).

In terms of safety, the BEACOPP regimen used in the HD2000 study resulted in higher rates of grade III-IV neutropenia (54%) and of

Table 1. Patient characteristics in each treatment arm of the two Italian trials.

	GISL trial		*FM-GITIL-IIL trial*	
	ABVD (n=99)	BEACOPP (n=98)	ABVD (n=166)	BEACOPP (n=155)
Characteristic	%		%	
Age ≥45 yr	18	17	23	20
Male gender	43	60	60	57
Nodular sclerosis histology	81	84	78	81
Bulky disease	31	37	55	61
International ≥3 prognostic score	30	43	54	55

Table 2. Estimate of 5 year survival rates by treatment arm in the two Italian trials.

	GISL trial		*FM-GITIL-IIL trial*	
	ABVD (n=99)	BEACOPP (n=98)	ABVD (n=166)	BEACOPP (n=155)
Variable	%		%	
Failure free survival	65	78	69	78
Progression free survival	68	81	69	85
Overall survival	84	92	86	87

severe infections (14%), compared with ABVD (34% and 2%, respectively). In the GISL trial BEACOPP chemotherapy had to be discontinued in 3 patients due to one case each of viral infection, candidiasis and hepatic dysfunction. In the FM-GITIL-IIL trial, BEACOPP chemotherapy had to be discontinued in 4 patients due to grade III-IV infections.

Interestingly, the adoption of a modified schedule did not substantially affect the efficacy of BEACOPP. In particular, the CR rates in the GISL and FM-GITIL-IIL trials compare favorably with the 96% reported by the GHSG for 8 cases treated with escalated BEACOPP. Similarly, patients treated with BEACOPP in the GISL trial achieved a 5-year PFS rate of 81% and in the FM-GITIL-IIL trial achieved a 5-year FFP rate of 85%, which are between the 75% and 85% 5-year FFTF rates previously observed for standard-dose and escalated-dose BEACOPP10, respectively. As far as treatment-related toxicity is concerned, patients treated with BEACOPP had more frequent severe events than the control arm, both in terms of neutropenia and infections. Overall, the adoption of a modified, less intensive schedule apparently increased the safety of the BEACOPP regimen. Thus far, few cases of secondary acute leukemia have been observed among patients treated with BEACOPP outside of the GHSG, although a longer follow-up is necessary to account for late relapses and secondary tumors. Although BEACOPP may be superior to ABVD in terms of PFS, mostly for patients with unfavorable advanced HL, it is still clinically mandatory to try to avoid unnecessary toxicity for those in the best prognostic group. At present, a response to treatment is considered to be the most important single prognostic factor for the individual patient, and FDG-PET imaging is emerging as a powerful tool to identify those patients with a suboptimal response to initial therapy. Response-adapted therapy, aiming to achieve high cure rates with minimal acute and delayed toxicity, is currently therefore a concrete possibility and is being investigated in several ongoing trials, the results of which will probably allow the use of the BEACOPP regimen only in patients not achieving an early response with the less toxic and more manageable ABVD.

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