Advanced and Relapsed/Refractory Hodgkin Lymphoma: What Has Been Achieved During the Last 50 Years

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During the last 50 years there has been great progress in understanding the biology of Hodgkin disease, which is now called Hodgkin lymphoma (HL), since it has been definitely shown to be a lymphoid neoplasm and its B-cell origin has been documented in the vast majority of cases. Progress in biology has also resulted in the identification of numerous biological prognostic factors, which may facilitate the definition of high-risk groups of patients and provide guidance for individualized therapy. Unfortunately, biological prognostic factors have not been incorporated in prognostic models applicable in everyday practice and need prospective validation. More importantly, during the last 50 years, advanced stage HL has been transformed from a rather incurable into a highly curable disease. Chemotherapy has gradually improved in terms of efficacy. MOPP was replaced by the more efficacious and less toxic ABVD regimen, but higher cure rates with BEACOPP-escalated have come at the expense of increased toxicity. Better risk stratification, probably based on early, interim positron emission tomography (PET) evaluation, may in the near future better identify those patients who really need intensified chemotherapy. Furthermore, the intensification of chemotherapy and the optimal use of PET at the end of chemotherapy have already minimized the use of radiotherapy in advanced disease, thus reducing the risk of long-term complications. Relapsed and refractory disease has also been rendered curable in almost half of the patients with the advent of effective salvage regimens, and, mainly, autologous stem cell transplantation. Furthermore, better understanding of the biology of HL has permitted the development of targeted therapy. Anti-CD30 targeting with brentuximab vedotin (BV) was the first targeted therapy to be approved for relapsed/refractory HL, either after autologous stem cell transplantation (auto-SCF) failure or after failure of two regimens in patients who were not candidates for transplant. Hopefully, the determination of the optimal role and timing of BV treatment and the development and approval of other targeted compounds will further improve the outcome of advanced stage as well as relapsed/refractory HL.
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Hodgkin's disease was described by Thomas Hodgkin in 1832 in his paper "On some morbid appearances of the absorbent glands and spleen."[1] It is now well recognized that Hodgkin's disease is a B-cell lymphoid neoplasm in the vast majority of cases and the term Hodgkin lymphoma (HL) has been adopted.

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Radiotherapy resulted in long-term survival in many patients with early stages of the disease. However, advanced stages remained largely incurable until the 1960s. Alkylating agent monotherapy with nitrogen mustard, sequential treatment with nitrogen mustard and chlorambucil, etc, resulted in clinical responses in many patients, albeit without clear evidence of potential cure since less than 10% of patients survived for 5 years free of disease.[2] MOPP (mechlorethamine, vincristine, procarbazine, prednisone) combination chemotherapy was the first treatment approach associated with high response rates and cure of a significant fraction of patients with advanced disease. Between 1964 and 1976, 188 patients were treated with MOPP, achieving a complete response rate of 84% and a 5-year relapse-free survival of 65%–70% for complete responders.[2–4]

Since then, the introduction of anthracyclines and the ABVD (Adriamycin, bleomycin, vinblastine, dacar-

bazine) regimen, further first-line treatment intensification with the BEACOPP (bleomycin, etoposide, Adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone) regimen, development of effective salvage regimens, and high-dose therapy with autologous stem cell transplantation (auto-SCT), effective risk stratification, incorporation of functional imaging in guiding therapy and early prognostic assessment, and, finally, the development of "targeted", biologic therapies, have revolutionized the treatment of HL. Thus, most patients with HL, including those with advanced disease as well as a fraction of patients with relapsed/refractory HL, are now curable. However, success has come at the expense of increased acute and long-term toxicity, so that the best balance between efficacy and toxicity needs to be achieved. A brief description of the progress made in the field of advanced stage and relapsed/refractory HL will be attempted in this review.

ACHIEVEMENTS IN THE TREATMENT OF ADVANCED DISEASE

The Evolution of Chemotherapy for Advanced HL

Advanced-stage HL, defined as stage Ann Arbor stage III and IV (since the classification of stage IIB is controversial), was almost always incurable until the introduction of the MOPP by De Vita and coworkers.[3,4] In the early 1970s, Bonadonna and coworkers developed the ABVD regimen,[5,6] which became the standard of care until the start of the 21st century and even now. ABVD proved to be superior to MOPP[6] and this was firmly established in a well-known Cancer and Leukemia Group B (CALGB) trial,[7] at least in terms of failure-free survival (FFS).

Based on the long-term results of the above CALGB trial, the 20-year FFS after ABVD without radiotherapy in stage III/IV HL is just above 40% (*v* 61% at 5 years), while the 20-year overall survival is 50%–55%. The corresponding figures for MOPP without radiotherapy are approximately 30% (*v* 50% at 5 years) and 40%, respectively.[8] However, when interpreting these figures, one should keep in mind the exact definition of FFS: deaths of any cause are considered as events in this analysis, even if relapse has not occurred.[7] Obviously FFS and tumor control rates are not synonymous; instead they may differ substantially, especially after long follow-up times. In fact, 15-year tumor control rate after ABVD plus radiotherapy in selected patients is in the order of 60%–65%.[9] However, even this figure is not satisfactory, since 35%–40% of the patients will ultimately require salvage therapy and almost half of them will succumb to the disease.

Several efforts to overcome drug resistance by alternating cycles of MOPP and ABVD,[7,8,10–12] creating hybrid regimens (MOPP/ABV and similar),[10–14] or including even more drugs,[15–17] were not successful despite very promising initial results. Indeed, these regimens were not superior to ABVD or equivalent regimens in randomized trials.[7,8,10–17]

Stanford V, a multidrug regimen with reduced gonadal toxicity and leukemogenicity, which incorporated radiation as a major component of treatment, was developed at Stanford in the late 1980s. Although initial results were impressive,[18] recent randomized trials failed to show any superiority over ABVD, even if the whole program including radiotherapy was strictly applied.[15,19,20]

During the 1990s, the German Hodgkin Study Group (GHSG) revolutionized the treatment of advanced HL with the development of BEACOPP-escalated.[21] The design of this dose- and time-intensified seven-drug regimen was based on animal studies, retrospective data, and mathematical models, suggesting that more rapid chemotherapy administration could improve 5-year FFS by 3% and moderate dose escalation by an additional 10%.[22,23] The HD9 trial, published in 2003, was the first one to show the superiority of a new regimen over an ABVD-equivalent, the alternating COPP/ABVD (cyclophosphamide, vincristine, procarbazine, prednisone/ABVD) regimen, which was extended not only to FFS but to overall survival as well.[23] HD9 was applicable to patients up to 65 years old with stage IIB X/E, III, or IV HL. Its mature results revealed an absolute 18% superiority of BEACOPP-escalated over COPP/ABVD at 10 years in terms of FFS, which was also translated to an 11% absolute difference in overall survival.[24] However, acute and long-term toxicity of BEACOPP-escalated was not negligible: grade 3/4 hematologic toxicity was much more frequent, 1.7% of the patients died of complications of chemotherapy, while a further 3% developed secondary myelodysplastic syndrome (sMDS) and acute non-lymphoblastic leukemia (ANLL), an almost uniformly fatal complication (Table 1; 10-year cumulative incidence, 3.2%). Among 14 cases of sMDS/ANLL, nine (64%) were diagnosed within the initial 5 years, four (29%) between 5 and 7 years, and one (7%) beyond 7 years from randomization.[24]

In an effort to reduce toxicity while maintaining efficacy, the HD12 trial of the GHSG compared eight cycles of BEACOPP-escalated with four cycles of this regimen plus four cycles of BEACOPP-baseline. Efficacy was similar in the two arms, but the expectations of reduced toxicity were not fulfilled (Table 1).[25] Although acute hematologic toxicity was lower in the second part of the de-escalated regimen and sMDS/ANLL appeared to be less frequent compared to HD9, overall, toxic death, and sMDS/ANLL rates were similar between the two chemotherapy arms (Table 1). In the