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CD30-positive malignant lymphomas: time for a change of management?

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In this issue of Haematologica, Zinzani *et al.* describe their experience with the anti-CD30 antibody-drug conjugate brentuximab vedotin in patients with relapsed/refractory Hodgkin's lymphoma. A total of 65 heavily pretreated patients who had been treated in a named patient program in nine Italian centers were analyzed.[1] Overall, 70.7% of these patients responded with 21.5% achieving complete remission. The progression-free survival rate at 20 months was 24.2% while the overall survival rate was 73.8%. Given the extensive pre-treatment with a median of four prior chemotherapy regimens, autologous or allogeneic stem cell transplantation in 92.3% of patients, and more than 50% refractory to their most recent therapy, these results are encouraging and in line with similar reports by other groups. Importantly, the treatment was also well tolerated. There is an additional short report in this issue in which Sabattini *et al.* describe CD30 expression in peripheral T-cell lymphomas.[2] They report that 43.2% (83/192) of the cases investigated expressed CD30. These data contribute to the growing body of evidence on a changing landscape in the treatment of CD30-positive malignant lymphomas.

Since the initial description of monoclonal antibodies against Hodgkin and Sternberg-Reed (HRS) cells in Hodgkin's lymphoma,[3,4] the CD30 antigen has attracted substantial scientific interest. Initially termed Ki-1, this antigen was clustered as CD30 showing a very strong expression on the malignant cells in Hodgkin's lymphoma. Importantly, only a few activated lymphocytes and eosinophils physiologically express this antigen and there is very little cross-reactivity with vital organs.[5,6] Shortly thereafter, CD30 was also found on the malignant cells of anaplastic large cell lymphoma (ALCL) and other malignant lymphomas. ALCL is an aggressive T-cell lymphoma representing about 1% of all lymphatic neoplasias.[7] Whereas in tissue samples from patients with Hodgkin's

lymphoma only about 1% of the nodal infiltrate represents HRS cells, the malignant cells in ALCL tissue are more densely packed. The CD30 antigen was subsequently also detected in mediastinal B-cell lymphoma, immunoblastic lymphoma, adult T-cell lymphoma and leukemias, mycosis fungoides, multiple myeloma, germinal center lymphoma, thyroid carcinoma and malignant mastocytosis. In addition, it could be demonstrated that CD30 is also present at a high density in patients with relapsed or refractory Hodgkin's lymphoma.[8,9]

Another paper published in this issue of the journal describes the molecular and phenotypic features common to CD30-positive peripheral T-cell lymphomas, and significant differences between CD30-negative and CD30-positive peripheral T-cell lymphomas, not otherwise specified, suggesting that CD30 expression might delineate two biologically distinct subgroups within this heterogeneous category. The putative clinical relevance of these subgroups could be the potential benefits of incorporating anti-CD30 immunoconjugates into the treatment strategies of CD30-positive peripheral T-cell lymphomas, not otherwise specified.[10]

A number of murine monoclonal antibodies against CD30, both in native form or linked to a variety of different toxins including ricin A-chain, radioisotopes or cytostatic drugs, were evaluated for their therapeutic effects in clinical trials of patients with Hodgkin's lymphoma.[11,12] However, most of these first- and second-generation anti-CD30 immunoconjugates were either too immunogenic or not effective enough for further clinical development.[13] In addition, human or humanized monoclonal antibodies against CD30 also gave disappointing clinical results.[14,15]

The landscape changed dramatically with the advent of brentuximab vedotin (formerly SGN-35). This antibody-drug conjugate consists of a humanized monoclonal antibody targeting CD30 that is linked via a protease-sensitive dipeptide to monomethyl-auristatin-E, a potent cytostatic tubulin inhibitor. Upon binding to the target antigen, brentuximab vedotin is internalized and subsequently degraded within the lysosomal compartment.[16] This mechanism of action explains the high specific potency of this construct, both in preclinical *in-vitro* models as well as in animals bearing human Hodgkin's and other CD30-positive xenografts.[17,18]

Based on the excellent preclinical results, brentuximab vedotin was subsequently evaluated in a phase I multicenter dose-escalation study in patients with Hodgkin's lymphoma and other CD30-positive lymphomas.[19] The drug was administered at doses of 0.1 to 3.6 mg/kg every 3 weeks to 45 heavily pretreated patients (42 with Hodgkin's lymphoma, 3 with other lymphomas), and was surprisingly effective with 17 objective responses including 11 complete remissions. The maximum tolerated dose was 1.8 mg/kg. At this dose level, 6/12 patients responded. Importantly, the drug was also very well tolerated with neutropenia and peripheral neuropathy as the most relevant side effects. In a subsequent phase II study, brentuximab vedotin was evaluated in a total of 102 patients with CD30-positive Hodgkin's lymphoma who had relapsed after or were refractory to autologous stem cell transplantation. Nearly all patients responded; the overall response rate was 75% with complete remissions in 34% of the patients.[20] The median duration of response for patients achieving complete remission was 20.5 months. After an observation time of more than 2 years, 65% of patients were free of progressive disease; the progression-free survival was 21.7 months and the overall survival of these patients had not been reached.[21] The drug was well tolerated; the most frequent WHO grade III/IV toxicities included neutropenia in 20% of patients and peripheral sensory neuropathy in 9%. Based on the heavy pretreatment and the refractory nature of the disease in most of these patients, this drug is very likely the most effective single agent available for the treatment of Hodgkin's lymphoma.

Given its rather poor prognosis and the uniform strong expression of CD30, systemic ALCL was also chosen for a phase II study with brentuximab vedotin. In this trial, 58 pretreated ALCL patients were treated with brentuximab vedotin at a dose of 1.8 mg/kg intravenously every 3 weeks in an outpatient setting. Overall, 50/58 patients (86%) achieved an objective response with 57% having complete remissions. The median duration of overall response and complete remission were 12.6 and 13.2 months, respectively.[22] Although this was a population of older patients, the tolerability in this trial was similar to that observed in the pivotal Hodgkin's lymphoma trial. As regards tolerability, 21% of the patients experienced grade III/IV adverse events, 14% had thrombocytopenia, and 12% had peripheral sensory neuropathy. On the basis of these clinical trials, the American Food and Drug Administration (08-2011) and the European Medicines Agency (10-2012) approved brentuximab vedotin as Adcetris® for the treatment of adult patients with relapsed or refractory CD30-positive Hodgkin's lymphoma following autologous stem cell transplantation or at least two prior therapies when multi-agent chemotherapy is not a treatment option. Adcetris® was also approved for the treatment of adult patients with relapsed or refractory systemic ALCL.

After more than 30 years without innovative new drugs registered for Hodgkin's lymphoma, the advent of brentuximab vedotin clearly marks a major event for this lymphoid malignancy. Patients with relapsed or refractory Hodgkin's lymphoma have become rarer in recent years, particularly in those countries in which more effective first-line treatment with BEACOPP-escalated[23] is being used. Thus, clinical trials in this setting have become more difficult. Although reports such as the one by Zinzani *et al.*[1] and others[24,25] on their experience with brentuximab vedotin can be helpful for better understanding the strengths and weaknesses of this new drug in daily clinical practice, a number of key questions still remain. One of the most burning questions is: Can we cure relapsed and refractory lymphoma patients with brentuximab vedotin alone? Other unanswered questions include the optimal number of cycles to be given in relapsed and refractory patients, the role of brentuximab vedotin as maintenance in high-risk patients and the challenge brentuximab vedotin poses to allogeneic transplantation. Given the limited number of patients and trials in this setting, most of these issues will probably remain unresolved for a considerable amount of time.

Clearly, brentuximab vedotin has already changed our treatment approaches in relapsed and refractory CD30-positive Hodgkin's lymphoma and ALCL. Still, there are a

number of new and possibly even more relevant questions to be addressed including the use of the drug in earlier stages of disease and its effectiveness in other CD30-positive lymphoid malignancies. These areas will soon be in the spotlight and are likely to become the next focus of clinical research with brentuximab vedotin. There are a number of currently ongoing clinical trials that are investigating the use of this new drug in other CD30-positive malignancies as well as earlier in the disease course. One of the next potential management-changing data set to emerge could be from the AETHERA trial in which patients with relapsed Hodgkin's lymphoma at high risk were randomized to receive either 16 courses of maintenance with brentuximab vedotin or placebo (*clinicaltrials.gov identifier: NCT 01100502*).

The even more relevant focus of clinical trials with brentuximab vedotin is, however, the combination of this drug with chemotherapy in different contexts. A recently performed phase I study demonstrated that the combination of ABVD and brentuximab vedotin resulted in a very high number of patients experiencing lung toxicity[26] so that combining this drug with bleomycin must be avoided. In contrast, combining a bleomycin-deleted ABVD variant with brentuximab (AVD-A) was shown to be both safe and effective in patients with previously untreated Hodgkin's lymphoma, ALCL and other CD30-positive lymphomas.[27] Currently, the AVD-A combination is being compared with ABVD in a prospectively randomized phase III trial *(clinicaltrials.gov identifier: NCT 01712490*). In addition, two different BEACOPP variants incorporating brentuximab vedotin are currently being compared in a multicenter setting (EudraCT Number: 2011-005082-21). The next logical step will be to challenge radiotherapy with brentuximab vedotin in patients with early-stage disease. Randomized clinical trials for this largest group of Hodgkin's lymphoma patients are currently being discussed. Together with the vast number of other trials using brentuximab vedotin in patients with CD30-positive malignancies, clearly the management of patients with these malignancies is subject to further changes.

In conclusion, these are interesting times not only for those dealing with malignant lymphomas. The advent of brentuximab vedotin introduced a new class of effective antibody-based constructs for a much more selective treatment of these and other malignancies. Similar constructs such as trastuzumab emtansine (T-DM1) in patients with breast cancer[28] have further highlighted the substantial potency of targeted antibody drug conjugates in oncology. We need smart trials to fully evaluate the role of these constructs for the sake of our patients.

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What challenges remain in chronic myeloid leukemia research?

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In the last fifteen years, the advent of imatinib has opened a new era in the treatment of CML. The challenge now is to eradicate the disease. To do this, groundbreaking scientific and biological studies should lead to the development of new techniques that can eliminate the last leukemic cells. Some of the salient future possibilities are summarized here.

Initial choice of therapy

Imatinib was introduced in 1998 and has until now been the preferred first-line therapy for newly diagnosed CML patients. Unfortunately, approximately 30-35% of the patients who receive this drug do not respond optimally or its administration has to be interrupted because of side effects. Nilotinib and dasatinib have been used as a second-line therapy. Both these agents can induce complete cytogenetic responses (CCyR) in approximately 50% and major molecular remission (MMR) in 20-30% of imatinib resistant patients.[1,2] When these drugs were compared with imatinib as initial treatment in two randomized clinical trials,[3-5] the responses were faster and superior with deeper molecular responses than with imatinib. Moreover, nilotinib and dasatinib were active also against different kinase domain mutations, even though neither drug inhibited clones with the T315I mutation. In general, both these drugs have good tolerability, though nilotinib showed a higher incidence of gastrointestinal toxicity than imatinib, while dasatinib induced more pleural effusions and more myelosuppression. Nilotinib and dasatinib induced more early responses, and this suggested the possibility of an improved progression-free survival (PFS) and overall survival (OS) that may be significant. In practice, this expectation was not born out and there is now a considerable body of evidence suggesting that there is no additional benefit from achieving these molecular targets in terms of overall survival (OS) or PFS.[6-10] For this reason, no specific tyrosine kinase inhibitor (TKI) should be preferred over the others solely on the basis that it induces a higher proportion of molecular responses.[6] Are there any clinical factors that may influence the choice of first-line therapy? There is no doubt that the outcome of imatinib is worse in high-risk patients. These findings could justify the earlier use of nilotinib or dasatinib in these patients.[11,12] In conclusion, which is the best TKI? As recently stated, many think that "better" means "more effective".[16] If this is the case, there is no doubt that nilotinib and dasatinib are better. But if we consider other factors such as tolerability and/or toxicity, the situation may change and we should evaluate how many patients are still taking the drug at a given time point.[6] If a clinician would like to prescribe imatinib, he or she should do so only if the patient is evaluated for cytogenetic and early molecular response (3 months). Patients who do not achieve complete hematologic remission (CHR), CCyR and early molecular response should be switched to a 2nd generation TKI. Nilotinib and dasatinib both appear to be more effective than imatinib but this superiority must be confirmed over the next few years. The length of the observation time that shows the durability of the response and the lack of severe adverse events may count in favor of imatinib.

Minimal residual disease and discontinuation of therapy

Discontinuation of imatinib is currently an investigational therapeutic approach for patients with chronic phase (CP)-CML in prolonged complete molecular remission (CMR), defined here as a 4.5-log reduction in BCR-ABL/ABL levels and undetectable transcripts using reverse transcriptase quantitative polymerase chain reaction (RTQ-PCR). In 2007, the French team reported a pilot study to evaluate the feasibility and safety of imatinib discontinuation in patients in CMR for more than two years. They observed that half the patients experienced a molecular relapse during the six months following treatment discontinuation.[13] All patients in molecular relapse were re-treated with imatinib and regained CMR. No late molecular relapses were observed in the remaining patients with an extended follow up of more than