High-risk relapsed or refractory classic Hodgkin lymphoma cure: how to make the impossible possible

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In the Article published in *The Lancet Haematology*, Alex Herrera and colleagues[1] report the results of a prospective study that aimed to assess the activity of consolidation therapy with brentuximab vedotin plus nivolumab starting 30–60 days after autologous haematopoietic stem-cell transplantation (HSCT) in a small cohort of 59 patients with high-risk relapsed or refractory classic Hodgkin lymphoma. The study, after a mean follow-up of 29·9 months, showed good outcomes in having long-term disease control in more than 90% of the patients. The study design adopted the same criteria for the definition of high-risk relapsed or refractory classic Hodgkin lymphoma as the randomised prospective AETHERA trial,[2] which showed the superiority of brentuximab vedotin consolidation after autologous HSCT compared with autologous HSCT alone in long-term disease control in high-risk relapsed or refractory classic Hodgkin lymphoma.

The AETHERA trial—beside confirming the high efficacy of post-autologous HSCT consolidation treatment with brentuximab vedotin in terms of a 2-year progression-free survival in as much as of 63% for patients included in the trial—had the high merit of proposing a well defined set of prognostic or predictive factors to identify patients at risk of not responding to rescue treatment with autologous HSCT after the failure of first-line chemotherapy. These factors comprised the following: refractory disease or disease relapsing within 12 months of completion of frontline treatment, only partial response or stable disease as best response to salvage therapy pre-autologous HSCT, two or more previous salvage therapies, and extra-nodal disease and B symptoms after failure of frontline therapy before autologous HSCT. Briefly, from 2010 to the end of 2012, 329 patients were randomly assigned to receive brentuximab vedotin 1·8 mg/kg intravenously once every 3 weeks with the best supportive care, versus placebo plus best supportive care, for up to 16 cycles, 30–45 days after autologous HSCT. After a median follow-up of 5 years, the benefit of brentuximab vedotin was more pronounced in patients with additional pre-autologous HSCT risk factors; the 5-year progression-free survival hazard ratio was 0·424 (95% CI 0·302–0·596) in 144 (87%) of 165 patients with two or more risk factors and 0·390 (0·255–0·596) in 82 (50%) of 165 patients with three or more risk factors.[3]

The same criteria for high-risk relapsed or refractory classic Hodgkin lymphoma definition in patients undergoing autologous HSCT as salvage treatment has been used by Herrera and colleagues.[1] After a median observation time of 2 years, the progression-free survival was 94% (95% CI 67–99) in patients with one risk factor, 96% (73–99) in patients with two risk factors, and 85% (51–96) in patients with three or more risk factors.[1] For the first time, a long-term and sustained response in patients undergoing autologous HSCT for high-risk relapsed or refractory classic Hodgkin lymphoma has been reported in most of the treated patients.

To assess the clinical value of Herrera and colleagues' study in the overall management of Hodgkin lymphoma, two main questions arise: how can high-risk relapsed or refractory classic Hodgkin lymphoma be defined in today's clinical practice? And, what is the effect in numerical terms of a rescue treatment ensuring long-term disease control for Hodgkin lymphoma

	Patient related	Disease burden related	Disease biology related
RisPACT trial	ECOG score >1	Stage IV disease Bulk tumour size >5 cm	Time to relapse <3 months Chemo-refractoriness at relapse
AETHERA trial	Extra-nodal spread at relapse*	Extra-nodal spread at relapse	Primary refractory or relapse <12 months Partial response or stable disease after second-line therapy Two or more lines of treatment B symptoms after first-line treatment failure

*Disease spread possibly related to loss of immunosurveillance of the patient.

Table: **Prognostic factors for patients with relapsed or refractory classic Hodgkin lymphoma**

failing a modern first-line treatment of Hodgkin lymphoma disease?

To answer the first question, in 2014, the RisPACT (Risk Factors for Post-Autologous HSCT outcome) prognostic score was retrospectively proposed for predicting progression-free survival after autologous HSCT for relapsed or refractory classic Hodgkin lymphoma from an analysis of 23 potential risk factors in a cohort of 1045 patients with Hodgkin lymphoma included in six prospective clinical trials. Stage IV disease, time to relapse of 3 months or less, ECOG performance status score of 1, tumour bulk of 5 cm, and inadequate response to salvage chemotherapy were significant and non-redundant risk factors for progression-free survival.[4,5] Notably, the proposition of prognostic factors in AETHERA is a conceptual evolution of the RisPACT factors, where tumour burden-related factors (stage IV and tumour bulk) have been replaced by surrogate factors of tumour spread and aggressiveness (extra-nodal spread and B symptoms) at the time of relapse, and prospectively validated (table).

The shift from anatomical to functional imaging to portray tumour burden in daily clinical practice was made possible by the widespread use of FDG-PET-CT instead of contrast-enhanced CT to diagnose and image relapse of Hodgkin lymphoma. Upon detection by PET-CT of functionally active residual disease, as well as extra-nodal disease spread (mainly bone or bone marrow), which were both undetectable with contrast-enhanced CT, prediction of autologous HSCT outcome with high accuracy is now possible.[6]

Second: what is the relapse rate of first-line treatment of Hodgkin lymphoma at the beginning of the third millennium? Moving from an expected treatment failure of 10% in early stage Hodgkin lymphoma and 15–20% in advanced stage Hodgkin lymphoma after first-line treatment, and upon assuming that early disease accounts for 40% and advanced disease accounts for 60% of PET-CT-staged Hodgkin lymphoma,[7] second-line Hodgkin lymphoma treatment is overall addressed to nearly 15% of the entire population of patients with Hodgkin lymphoma. Whether results obtained by Herrera and colleagues will be confirmed by a longer follow-up and in a larger series of patients, a second-line treatment that is able to induce prolonged disease remission in more than 95% of the patients is a milestone achievement in the overall treatment of Hodgkin lymphoma.

I declare no competing interests.

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Towards chemotherapy-free treatment of Philadelphia chromosome-positive acute lymphoblastic leukaemia

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The addition of tyrosine kinase inhibitors (TKIs) to conventional chemotherapy backbones for adults with newly diagnosed Philadelphia chromosome-positive (Ph-positive) acute lymphoblastic leukaemia has substantially improved treatment outcomes.[1,2] However, the long-term outcomes are still unsatisfactory, with treatment-related resistance and toxicity. Over the past 10 years, several clinical trials have incrementally shown improved outcomes and reduced toxicity for these patients. These steps include the upfront use of the