Editorial

To AVoiD bleomycin from Hodgkin's regimen?

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Abstract: To improve long-term results in advanced Hodgkin's lymphoma (HL) has been a continuous challenge from many years. Intensified chemotherapy regimen showed an advantage over standard regimen in terms of anti-tumoral activity, however haematological and non-haematological toxicities were significantly higher. Recently, brentuximab vedotin (BV) which is an antibody-drug conjugate targeting CD30 antigen, showed very promising results when given as single agent in patients with relapsed and refractory HL. Based on this hypothesis, Anas Younes and colleagues designed a phase I dose-escalation study in which BV was administered as front-line treatment either with the combination of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) regimen or AVD (ABVD without bleomycin). The aims of the study were to assess safety and efficacy of this drug in combination with chemotherapy in newly-diagnosed patients with advanced HL. The results showed that BV should not be given with bleomycin due to a high incidence of pulmonary toxicity. The trial also demonstrated that the combination of BV and AVD can be given safely and led to an impressive complete remission rate of 96%. Although we need to remain careful with these preliminary results, the data reported in the *Lancet Oncology* open a new therapeutic era in the field of HL, combining both less toxicity and higher efficacy.

Keywords: Hodgkin; chemotherapy; brentuximab vedotin (BV); safety; efficacy

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The combination of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) is the most widely regimen used in the treatment of patients with Hodgkin's lymphoma (HL). ABVD regimen still remains standard first-line chemotherapy for advanced HL with an acceptable toxicity. ABVD is well tolerated and toxic side effects are manageable. Fertility after ABVD is not compromised, and risk of developing second cancer is not increased (1). However, ABVD sometimes induce serious lung toxic effects due to bleomycin which could be fatal (2,3). ABVD is supposed to cure 70% to 80% of patients with advanced stage disease, while 20% to 30% of patients are refractory or relapse after reaching complete response (4,5). More than 50% of patients in failure can be successfully treated with high-dose chemotherapy and autologous stem cell transplantation (6).

Now and from a decade, the intensive BEACOPP escalated regimen (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) showed superior activity to ABVD in some randomized studies, and became a standard of care in advanced HL patients for many HL study groups (7). The majority of these studies showed an advantage for BEACOPP escalated over ABVD in terms of event-free survival but not for overall survival (4,5). More recently, a network meta-analysis reported a 10% survival advantage of six cycles of BEACOPP escalated over ABVD after five years of follow-up (8). However, acute haematological toxicity is significantly increased in patients receiving BEACOPP leading to a dose reduction in some patients. Late effects like secondary malignancies should also be considered although the high incidence of secondary myelodysplatic syndromes and acute myeloid leukaemia reported in the original report was not confirmed in consecutive trials.

Intensive regimen as BEACOPP escalated has been restricted to patients younger than 60 years in the majority

of the studies. However, patients older than 60 years account for approximately 20% of all HL patients. If ABVD can be considered as the treatment of choice in these patients, it has been recently demonstrated that four cycles of ABVD is associated with substantial dose reduction, treatment delay, toxicity, and treatment-related mortality (9).

Thus, new therapeutic strategies including novel drugs are needed for the treatment of HL, especially for patients who present with an advanced and aggressive disease, and those who are older and unfit. HL now beneficiates from targeted therapies, and brentuximab vedotin (BV) which is an antibody-drug conjugate, has shown very promising results. When given as single agent in patients with relapsed or refractory HL, BV was well-tolerated and could induce 75% of objective response and 35% of complete response in this poor-risk group of patients. The median duration of response in this series was less than nine months and subsequently supports the hypothesis to introduce such an active drug earlier in the disease (10).

In the *Lancet Oncology*, Anas Younes and his colleagues reported a phase I dose escalation study of BV combined with ABVD or AVD (ABVD regimen without bleomycin) in patients with newly-diagnosed HL. The aims of the study were to assess the safety and efficacy of BV when associated to either ABVD or AVD. The upper limit age in this series was 60 years, but the majority of patients had advanced disease. Pulmonary toxicity was the major side effect observed in the BV and ABVD group with 44% of patients who experienced lung injury, of whom two died. Authors concluded that concomitant use of BV and bleomycin is contraindicated because of increased incidence of pulmonary toxicity. BV at 1, 2 mg/kg combined with AVD given every two weeks was generally well-tolerated, and no pulmonary toxicity was reported in this group. Considering adverse events other than lung injury, BV was fully administered (12 cycles) in 15/25 (60%) patients receiving ABVD, and in 22/26 (85%) patients in the AVD group. The complete response rate was 95% in evaluable patients in BV and ABVD group and 96% in BV and AVD group, while one-year progression free survival was 85% and 95% respectively. Based on these impressive results, authors are now conducting a phase III study comparing BV + AVD versus ABVD alone in patients with newly-diagnosed HL (11).

Such results raise many questions about toxicity and efficacy of the main chemotherapy regimen used in the treatment of patients with advanced HL in the era of new targeted therapies. HL remains a curable disease even when patients present with an adverse international prognostic score. Whatever the chemotherapy regimen used, deaths after 20 years were shown to be related to treatment side effects and not to HL (12). Our challenge today is still to enhance results but also to decrease toxicity. The use of interim PET scan after two cycles of chemotherapy has been shown to be of high value prognostic for the risk of relapse and this might translate in better survival (13). To decrease intensity of chemotherapy after a negative interim PET scan is one of the major issues addressed in ongoing trials. On the other hand, the use of new targeted therapies as BV in combination with modified chemotherapy as front-line treatment will allow us to better deliver the treatment, and this should contribute to reduce the failure rate in HL and to improve long-term results. To avoid bleomycin from HL regimen represent one of the challenging issues we need to explore. Certainly, BV is now opening a new era of treatment in HL, as rituximab did in non-HL in the 2000's.

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