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LETTER TO THE EDITOR

Is radiotherapy still necessary for diffuse large B-cell lymphoma therapy?

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To the Editor,

Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive lymphoma subtype, accounting for approximately 30% of new cases of non-Hodgkin's lymphoma (NHL) [1]. Despite its aggressive clinical course, the addition of rituximab, a chimeric monoclonal anti-CD20 antibody, to standard first line therapy consisting of cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) leads to a five-year overall survival (OS) of up to 70% [2]. Another milestone in the management of DLBCL has been the introduction of positron emission tomography (PET), allowing for a better staging and evaluation of treatment response [3]. Despite these improvements, radiotherapy (RT) is still considered the standard of care for a subset of DLBCL patients. Nevertheless, RT is very stressful and often associated with quality of life impairing side effects [4,5]. However, intensity-modulated RT and other techniques of highly conformal RT, which reduce the amount of radiation delivered to surrounding areas, have become increasingly diffused. The risk of secondary malignancies is frequently contested as well [4,5]. Nonetheless, DLBCL occurs mainly in elderly patients, which is why there are few odds to see cancer development. Furthermore, in a study from the British Columbia Cancer Agency, only 14% of second malignancies developed within the radiation field. In addition, the development of these tumors was correlated with an underlying susceptibility of the patients rather than treatment [6]. Overall, up to now it is not yet clear if in the era of immunochemotherapy and PET, RT should still be delivered to all patients meeting the actual RT-criteria or if it should be reserved to a much smaller subgroup which does not achieve a complete response (CR) after first line treatment.

According to current guidelines patients affected by stage I-II DLBCL should undergo either six cycles of R-CHOP or three cycles of R-CHOP plus RT [7]. These recommendations are mainly based on the results of four large randomized trials performed in the pre-rituximab era [the Southwest Oncology Group (SWOG) 8736 trial, the Groupe d'Etudes des Lymphomes de l'Adulte (GELA) LNH 93-1 trial, the Eastern Cooperative Oncology Group (ECOG) 1484 study, and the GELA LNH 93-4 trial)] [5,8–10] and one including rituximab [11]. Overall, in the pre-rituximab era, shorter courses of chemotherapy plus RT seemed to be at least equal to six cycles of the same treatment alone [5,8,9]. In the SWOG8736 study this approach initially appeared to be superior in terms of five-year OS while after a longer follow-up this difference was not confirmed due to the high rate of relapses and subsequent lymphoma-related death in both arms [10]. As proved by us and others [11,12], although the addition of rituximab improved OS in DLBCL patients, relapses were not infrequent and probably a consequence of biological differences between limited- and advanced-stage lymphoma. We also provided some evidence – though based on a retrospective data – that in the rituximab era RT did not significantly contribute to a better outcome in stage I/II DLBCL patients [12]. Furthermore, the addition of rituximab failed to significantly improve

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the outcome of patients with skeletal involvement. However, event-free survival (EFS) was improved with consolidation RT to the site of skeletal involvement, regardless of disease stage [13]. In the last decade, PET scanning has demonstrated to be an efficient tool to evaluate the extension of disease and response to treatment in DLBCL [3]. Therefore it might be an appropriate technique to identify patients with persistence of the disease after immunochemotherapy in order to address them to consolidative RT. In particular, some retrospective studies have shown that PET-positive patients with fluorodeoxyglucose uptake confined to a limited area after primary therapy with R-CHOP seem to be the most appealing candidates [14,15]. An ongoing phase III clinical trial is evaluating the activity of three courses of R-CHOP plus RT versus six cycles of R-CHOP alone in localized DLBCL. In addition, an interim PET is planned after three cycles of chemotherapy in order to clarify its correlation with progression free survival (PFS) and OS. (NCT02054559). Overall, treatment of localized DLBCL needs to be improved and new treatment strategies are under investigation [16].

The second indication for RT in patients with DLBCL, according to current treatment guidelines, is the presence of bulky disease [7]. As bulky lesions are associated with an elevated local relapse rate [17] probably due to the persistence of minimal residual disease even when a clinical CR is achieved after immunochemotherapy, consolidation RT has been proposed to improve outcome. Many studies have demonstrated that RT has increased PFS and local disease control [18–21] as well as five-year OS in this subset [21–23]. In particular, RT consolidation seems to be crucial in bulky disease patients who did not achieve CR after R-CHOP thanks to its effect in eradicating isolated local residual lymphoma [24]. Although there are some cases of false positive PET due to metabolically active healing or persistent inflammation, a PET-based response assessment could allow to reduce the number of patients who should be directed to RT. However, its role remains unclear in PET-negative patients after first line treatment. Despite the increase in PFS, EFS and local control, only a trend toward improved OS has been reported with the combination treatment [18,19]. Consequently, RT consolidation seems to add very little when chemotherapy has achieved CR. However, considering the retrospective nature of these studies, the role of RT in this clinical context cannot be definitively demonstrated. Currently there are at least two prospective studies recruiting participants to assess the impact of RT on the clinical course of patients affected by DLBCL. The first one, a phase II clinical trial conducted by the Duke University (NCT01186978), is evaluating if radiation dose and treatment volume can be safely reduced from 30 Gy to 20 Gy in patients who have a negative PET scan following rituximab-containing chemotherapy. The second one, the German UNFOLDER phase III trial (NCT00278408), is currently appraising the impact of RT on patients with bulky and/or extranodal disease who undergo R-CHOP. At the interim analysis of this study excessive failures were observed when RT was omitted, forcing the early closure of the not irradiating arm.

In the past, some study protocols also considered extranodal disease in DLBCL as an indication for RT regardless of the presence of bulky disease [25,26]. However, up to now no clinical trial has confirmed the necessity of RT in this setting of patients. Indeed, in a recent retrospective analysis published by our study group we provide some evidence that RT might not be strictly necessary for patients with extranodal DLBCL [12,27].

In conclusion, the backbone of DLBCL treatment remains immunochemotherapy even though local relapse represents a frequent cause of treatment failure. RT shows to be an effective local therapy for DLBCL and its incorporation into the treatment of DLBCL needs to be considered. However, due to the advent of new drugs and disease evaluation methods such as PET, treatment strategies are evolving and new approaches considering reduction or omission of RT are under investigation.

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