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Assessing complete remission status in incurable follicular lymphomas, to what purpose?

We read with interest the article by Rutherford et al (2017) entitled “Bone marrow biopsies do not impact response assessment for follicular lymphoma patients treated on clinical trials.” Bone marrow biopsy (BMB) is routinely performed for staging follicular lymphoma and current guidelines recommend performing repeat BMB after treatment in all patients with a positive BMB at baseline in order to determine remissions status (Barrington et al, 2014; Cheson et al, 2014). This recommendation however, is questioned by Rutherford et al (2017). They report that patients with a positive baseline BMB and either partial response (PR), stable disease (SD) or progressive disease (PD) on imaging after treatment should not undergo repeat BMB, because these patients clearly have active disease regardless of BMB results. Consequently, BMB theoretically only has potentially useful diagnostic impact in follicular lymphoma patients who are in complete remission (CR) according to post-treatment imaging. In order to determine the proportion of follicular lymphoma patients in CR after treatment according to imaging studies, but with positive BMB, Rutherford et al (2017) analysed 99 patients with follicular lymphoma, of whom 45 (45.5%) had a positive BMB at baseline. Of these 45 patients, post-treatment imaging studies demonstrated 12 CR, 19 PR, 5 SD and 9 PD cases. Eleven of the 12 patients (91.7%) with CR according to imaging studies had a negative post-treatment BMB. One patient did not undergo post-treatment BMB despite having CR on imaging. At most, in only 1/99 patients (1.0%) included in their study, BMB would potentially have been relevant to assess response. On the other hand, in the 33 patients not in CR, 14 (42.4%) underwent BMB after treatment, of whom 7 (50%) were positive. In the remaining 54 patients with negative baseline BMBs, 11 (20.4%) underwent BMBs after treatment, all showing no lymphoma. Rutherford et al (2017) concluded that BMBs do not meaningfully impact response assessment in patients treated for follicular lymphoma. They suggest that developing response criteria for follicular lymphoma can omit bone marrow assessment without any evident loss of rigour. Although we agree with the authors’ conclusion that BMBs should not be performed after treatment in follicular lymphoma patients, several important comments have to be made. First, Rutherford et al (2017) did not adequately describe the methodology of their study, because they did not report how many cases underwent computed tomography (CT) or 18F-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) for response assessment. Note that both examinations are proposed for response assessment by current guidelines (Barrington et al, 2014; Cheson et al, 2014), but that FDG-PET is considered the standard of care (Barrington et al, 2014). Because this important information was not reported by Rutherford et al (2017), it remains unknown whether (the much more expensive) FDG-PET examinations provide useful information beyond those obtained by CT scans. Second, Rutherford et al (2017) did not report whether their imaging examinations were interpreted on a patient or local level. In other words, were BMBs results correlated to the (coincidental) occurrence of a CR in extramedullary lesions, or absence of infiltration of the bone marrow on imaging studies? Note that CT cannot evaluate the bone marrow and that several studies have already shown FDG-PET to have a very low sensitivity to detect bone marrow involvement at baseline [reported range: 34.3–54.2% (Le Dortz et al, 2010; Luminari et al, 2013; Wohrer et al, 2006)]. It is not unlikely that these results can be translated to the post-treatment setting, contradicting the conclusion of Rutherford et al (Rutherford et al, 2017). Even more striking...
are the results of a study performed by our research group in which BMB results were spatially correlated with FDG-PET results at the posterior iliac crest. In that particular study (Adams et al., 2014), of 8 patients with positive BMBs at baseline, FDG avidity was visually detected in the iliac crest in 0 cases (sensitivity of 0%).

Another important issue to discuss is that it is unproven whether response assessment, whether performed by imaging studies or with BMB, has any clinical value in follicular lymphoma at all. First, it should be noted that follicular lymphomas are generally incurable and that a CR, as assessed by (low sensitivity) imaging studies or BMBs, does not indicate cure. Recently, several studies have been published showing posttreatment FDG-PET results to be predictive of progression-free survival (PFS), but these studies suffered from methodological errors, the main being a lack of clear definition of end of PFS (Adams et al., 2016). Note that several criteria are used for this purpose: first clinical or radiological evidence of disease after attaining CR, progression of tumour volume in CT studies, increase in metabolic activity at FDG-PET examinations, development of symptomatic disease, changes in laboratory assessments, diagnosis of a high-grade transformation or death. These studies also showed FDG-PET to be inferior in predicting overall survival as compared to easily available (pre-treatment) prediction rules, such as the Follicular Lymphoma International Prognostic Index (FLIPI) (Solal-Celigny et al., 2004; Adams & Kwee, 2017), and that no study has shown FDG-PET after treatment to have any additional value to the FLIPI (Adams & Kwee, 2017). Finally, it is unlikely that response evaluation results (whether with BMB or radiological studies) add any clinically useful information, because patients with residual disease after treatment according to response criteria are generally not treated before redevelopment of clearly symptomatic disease during long-term follow-up.

In conclusion, the study by Rutherford et al. (2017) does not report whether FDG-PET adds useful information beyond CT in assessing bone marrow status after treatment in follicular lymphoma patients. Furthermore, the need for response assessment (both by BMB and with imaging studies) after treatment in follicular lymphoma is low, due to absence of clear clinical consequences of assessing post-treatment disease status.

Compliance with ethical standards

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Potential conflicts of interest

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Ethical approval

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Author contributions

Hugo J. A. Adams: study design, article writing, final approval of the manuscript. Thomas C. Kwee: study design, article writing, final approval of the manuscript.

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Autologous stem cell transplant and combination immunotherapy of rituximab and interferon-α induces prolonged clinical and molecular remissions in patients with follicular lymphoma

Chemo-immunotherapy followed by maintenance rituximab (R) improves progression-free survival (PFS) and overall survival (OS) in follicular lymphoma (FL) (Vidal et al, 2017). High-dose therapy (HDT) with autologous stem cell transplant (ASCT) at second or third relapse improves PFS and OS (Schouten et al, 2003) but relapses inevitably occur. Strategies combining R immunotherapy with HDT/ASCT are promising but there is minimal data on long-term outcome and toxicity. Interferon-α (IFN-α) improves PFS when administered with and after anthracycline-based front-line therapy (Rohatiner et al, 2005). Combining R with IFN-α is associated with fewer early treatment failures, when compared to single agent R (Kimby et al, 2015). We hypothesized that IFN-α may synergize with R and would minimize or eliminate minimal residual disease (MRD) post-HDT/ASCT, thus improving PFS and OS. To our knowledge, there are no published trials looking at this approach.

From July 2000 to September 2009, patients in first or second relapse with stage III or IV FL were enrolled in this phase II, prospective study. Salvage chemotherapy consisted of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) or DHAP (dexamethasone, high-dose cytarabine, cisplatin), if patients had received prior anthracycline. Three weekly infusions of R 375 mg/m² were administered as an in-vivo purge. Patients with ≥75% reduction in disease proceeded to HDT with CBV (cyclophosphamide, carmustine, etoposide) chemotherapy. IFN-α was commenced at 12 weeks post ASCT. Six weekly infusions of R 375 mg/m² were administered from week 14. Patients with polymerase chain reaction (PCR) markers of lymphoma had continued real-time quantitative PCR (RQ-PCR) monitoring for MRD by bone marrow (BM), peripheral blood (PB) and apheresed product (Figure S1, S2).

We present results on 30 patients. Univariate and multivariate analyses were conducted to identify significant predictors of OS and PFS. Results were compared to a prior prospective trial performed at our institution (Bernstein et al, 2015).

Thirty-six patients were enrolled, with a median age of 47 years. Sixty-seven percent had stage IV disease and 50% had a high FL International Prognostic Index score. The median remission duration pre-enrolment was 9 months. Eleven (31%) had received R prior to enrolment. Six patients were not transplanted (Table S1).

Twenty-three patients (77%) had a complete response (CR) at 3 months post-ASCT. Nine of 18 patients (50%) who achieved partial response (PR) post-salvage converted to a CR at 3 months post-transplant. Twenty-seven commenced IFN-α and 17 (63%) completed the intended 2 years of treatment (Table SII). Post-completion of maintenance, the CR rate remained at 77%. Three patients with a PR at 3 months converted to a CR post-maintenance. Seventy-six percent of this high-risk group remain alive at 10 years post-ASCT. Although the median OS was not reached (range 3–6–16.2 years), a survival plateau appeared at 8 years. The range of PFS was 0.7–15.2 years; the median is yet to be determined. A plateau appeared at 8 years, with 56% (17) of patients remaining disease-free (Fig 1).

Minimal residual disease was detected by RQ-PCR (Fig 2) in 22 (73%). Ten of 22 apheresed products had PCR detectable disease. Clinical and molecular remission was achieved during maintenance in 5 of 7 patients who were MRD positive at 3 months post-ASCT. There was good correlation between clinical response/relapse and MRD assessment on PB.

Variables to significantly affect OS were remission duration pre-enrolment ($P = 0.0252$, HR $0.250$ [univariate]) and ($P = 0.0216$, Hazard ratio [HR] $0.233$ [multivariate]), and secondary malignancy development ($P = 0.0504$, HR $4.452$).