A prospective study of the separate predictive capabilities of ^{18}[F]-FDG-PET and molecular response in patients with relapsed indolent non-Hodgkin's lymphoma following treatment with iodine-^{131}-rituximab radio-immunotherapy

Recent data have demonstrated the efficacy of anti-CD20 radio-immunotherapy (RIT) in patients with newly diagnosed advanced follicular non-Hodgkin's lymphoma (NHL).[1,2] A significant proportion of treated patients have extended event-free survival (EFS). Although there is as yet no clear pre-treatment indicator regarding which patients benefit the most, the EFS is related to the extent of remission achieved as assessed by CT. However, the ability of a molecular remission to predict outcome following radio-immunotherapy is unclear. These trials resulted in high molecular remission rates, with one reporting 81% of patients with both a complete remission (CR) and also Bcl-2 molecular response surviving to 5 years without disease progression. This paper presents the only data available to date concernng the ability of RIT to induce molecular responses in the setting of relapsed disease. ^{18}[F]-FDG positron emission tomography (PET) has emerged as a major imaging modality for Hodgkin's lymphoma and aggressive NHL.[3] Its excellent sensitivity and specificity has led to suggestions in recent data for a role for PET also in indolent NHL.[4]

We participated in a multi-center phase II trial of 131-I-labeled rituximab treatment of patients with relapsed or refractory indolent B-cell NHL.[5] This report presents prospectively collected data on PET and molecular response assessment for patients treated at our institute. Baseline and surveillance PET were performed, as well as bone marrow (BM) and peripheral blood (PB) analysis for the Bcl-2 rearrangement in patients with follicular lymphoma, in order to separately assess the correlation of PET and that of molecular remission status with duration of response. Patients over 18 years old with relapsed or refractory indolent B-cell NHL and an adequate bone marrow reserve (neutrophils >1.5×10^9/L and platelets >100×10^9/L) were eligible for treatment. The percentage of bone marrow involvement was not an exclusion criterion for treatment. PET and CT scans were performed at baseline and three months to assess metabolic response. Interpretation of these scans was performed according to the International Harmonization Project in Lymphoma criteria.[6] In patients with follicular lymphoma, a polymerase chain reaction (PCR) with a sensitivity of 1 in 10^4 for the Bcl-2 rearrangement was performed on BM and PB at baseline. If either were positive, repeat BM and PB samples were taken at three months. Metabolic and PCR responses to ^{131}I-rituximab were then examined for influence on EFS and OS. Twenty-nine patients from our center were enrolled in the study (Table 1). All but one patient with grade 1 follicular lymphoma were PET avid at baseline, while one patient had no follow-up PET scans performed. CT categorized response in these patients. An objective response by PET was observed in 24 patients (82.8%) with a complete metabolic response (CMR) at <three months in 15 patients (58.3%). In patients with follicular NHL, there was an overall response rate (ORR) of 87.5% and CMR of 60.9%. The three-month PET scan predicted TTP, with a median of 15 months for patients in CMR (n=15), 11 months for partial metabolic remission (PMR) (n=7) and three months for those not achieving PR (n=5)(p=0.001) (Figure 1A). Three patients remain in CMR at 59+, 65+ and 65+ months. One other patient died in CMR at 15 months due to melanoma. Three-month CT also predicted outcome, but with a less statistically significant separation of the patient groups, and a median TTP of 24 months for patients in CR (n=9), 12 months for PR (n=10) and six months for those not achieving PR (n=9) (p=0.002). For the 10 patients in PR by CT at three months, a positive contemporaneous PET scan predicted earlier progression; median TTP was nine months for the 4 patients in PET PMR, and 14 months for the 6 patients in PET CMR (p=0.032) (Figure 1B). Twenty patients are still alive, with a median follow-up of 47 months. Two patients died of unrelated malignancies and one from secondary acute myeloid leukemia following autologous stem cell transplantation for progressive disease. Twenty-one patients had evaluable baseline molecular data, and 11 were positive for the Bcl-2 rearrangement. At three months, 5 patients (45%) became PCR negative in PB and BM with a median TTP of 24 months, while 6 remained PCR positive, with a median TTP of six months (p=0.0025) (Figure 1C). We present contemporaneous PCR and PET response assessment in patients following RIT for relapsed indolent NHL. We observe that I-131-labeled rituximab RIT is able to induce complete metabolic and molecular responses in this patient cohort. Similar observations were made with other types of RIT in the same patient group. We confirm emerging evidence of high sensitivity of PET in patients with indolent NHL.[4] PET response assessment following RIT has been limited to case reports only, but it does suggest it is possible to achieve CMR.[7] Of the patients who achieved a PMR or CMR by PET criteria, 11 out of 22 (50%) have had a remission that has outlasted their previous remission duration. For patients who achieve a CT PR, it appears that response according to PET can stratify patients into risk groups for relapse. Furthermore, PET scan status at three months may predict EFS more accurately than CT. Whether PET negativity should be the therapeutic goal of treatment is unclear, and this should be the focus of future trials. As previous studies have shown, a significant proportion of patients following RIT have extended EFS,[1] although there is, as yet, no clear pre-treatment indicator regarding which patients benefit the most.

Table 1. Patients' characteristics (n=29).

Age	Median 60 years (38-72)
Histology	f.NHL 24, SLL 2, MZNHL 3
Median time from diagnosis (months)	43 (range 13-173)
Median n. of prior treatments	3 (range 1-7)
Previous rituximab	10 single agent 8 combination
Median time from last treatment	22 months (1-73)
BM histologically involved	11 (9 pts. with f.NHL)
FLIPI (for f.NHL patients)	0-1-3, 2-8, 3 or more 13

f.NHL: follicular lymphoma; SLL: small lymphocytic lymphoma; MZNHL: marginal zone lymphoma; BM: bone marrow; FLIPI: Follicular Lymphoma International Prognostic Index.

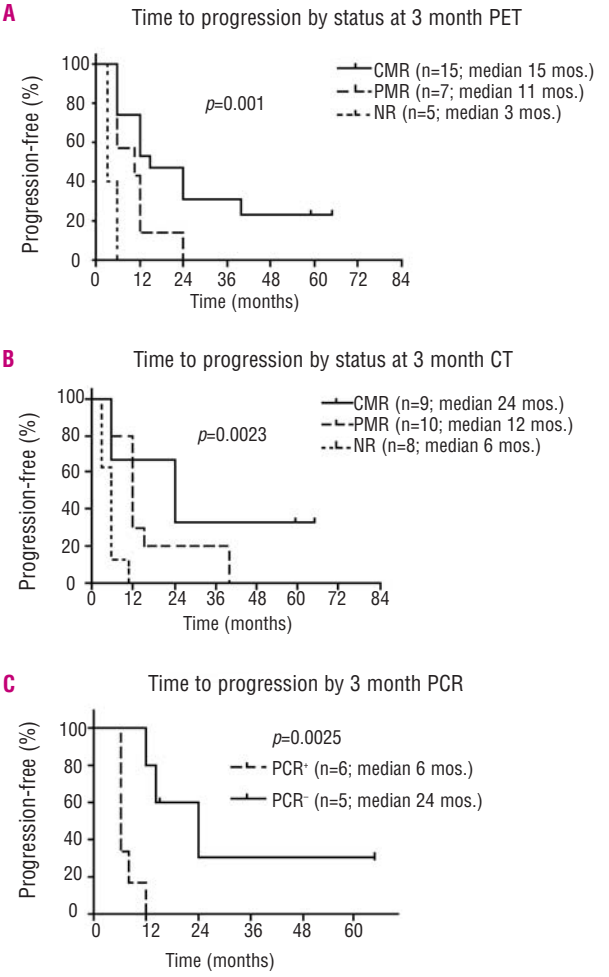

Figure 1. (A) **Time to progression in all patients by response to 3 month PET scan,** (B) **Time to progression in all patients by response to 3 month CT scan,** (C) **Time to progression by molecular response in patients with follicular lymphoma. CMR: complete metabolic response; PMR: partial metabolic response; NR: no response; CR: complete remission; PR: partial remission; PCR: polymerase chain reaction.**

Our data suggest that all durable responders must have attained a PET CMR at three months. The significance of molecular response following treatment for follicular lymphoma is difficult to interpret, partly due to the lack of a standardized method. It is generally accepted that a molecular response is associated with a superior EFS.[8] Using our non-quantative assay, it appears that patients who become PCR negative in PB and BM have a significantly prolonged TTP. Whether BM or PB should be used is unclear, with inferior results for PB in some studies.[9] Other potentially confounding issues include very low levels of Bcl-2 rearrangements in healthy subjects without follicular lymphoma which are expected to be below the level of sensitivity of our assay, and the use of monoclonal antibody therapy. It may be that a molecular CR in BM and PB in patients with high detectable levels of the Bcl-2 rearrangement pre-treatment corresponds to prolonged TTP. It is unclear whether the detection of residual lymphoma cells by PCR should be an indication to continue therapy, even in younger patients.[10]

To summarize, we have demonstrated that single agent I-rituximab can induce complete metabolic and molecular remission, and the separate predictive capabilities of ^{18}[F]-FDG-PET and molecular response to predict response duration in patients with relapsed indolent NHL. Furthermore, a proportion of these patients have extended EFS. PET response assessment could be promising in predicting which patients are likely to attain durable benefit from RIT.

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