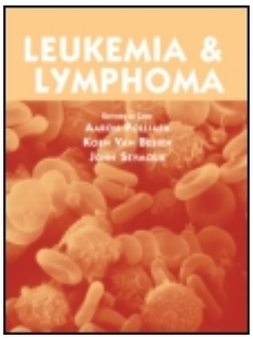

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COMMENTARY

Left behind: should minimal residual disease be treated in hairy cell leukemia?

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Remarkable advances have been made in the treatment of hairy cell leukemia (HCL) since its initial description by Bouroncle *et al*. in 1958 [1]. In the mid-1980s, the effectiveness of interferon α was first reported in HCL [2], followed by reports of striking therapeutic activity of both purine nucleoside analogs pentostatin [3] and cladribine [4]. Subsequent larger long-term follow-up studies have confirmed that 80–90% of patients can achieve a complete remission (CR) with either cladribine or pentostatin [5–8]. However, despite the high remission rate and long disease-free survival, relapse rates up to 37% in long-term follow-up suggest the presence of minimal residual disease (MRD) in a substantial number of patients following the initial purine analog-based therapy [5,6].

In this issue of ***Leukemia and Lymphoma***, the Spanish Cooperative Group on Chronic Lymphocytic Leukemia (GELLC) report a retrospective analysis of 107 patients with HCL treated with either pentostatin ($n = 27$) or cladribine ($n = 80$) [9]. They observed a similar CR rate among patients treated with pentostatin and cladribine, 92% and 88%, respectively, when assessed at completion of pentostatin treatment and 2–3 months after completion of cladribine. MRD was studied in 82 patients using multiparameter flow cytometry, and was detected in 52% and 47% of patients in CR who received pentostatin and cladribine, respectively. Persistent MRD was associated with a shorter treatment-free interval (97 months vs. not reached), and the authors have suggested that therapeutic strategies to eradicate MRD may lead to longer remissions.

The implication of MRD in HCL remains a controversial issue. First, there is no standardized method to define MRD. Investigators have used a variety of methods including immunophenotyping by flow cytometry, immunohistochemical stain (IHC) and polymerase chain reaction (PCR) with different sensitivities of detection, and reported MRD rates of 13–80% in patients who remain in stable CR [10–15]. Second, the optimal time to evaluate the maximal benefit of purine analogs is unknown, and MRD assessment has been performed at various time points ranging from 1 to 6 months after completion of therapy. Third, the clinical significance of MRD is unclear. While some studies have reported that MRD predicts relapse [14–16], others have failed to confirm the association of persistent MRD and relapse risk [13,17]. In fact, the study by Sigal *et al*. showed that at 18 years after diagnosis, 50–60% of patients who remain in CR after a single course of treatment with cladribine still have MRD [13]. Since many patients with MRD and even overt morphologic evidence of disease in the marrow do not clinically relapse, it is uncertain whether more aggressive front-line therapeutic strategies will improve the long-term outcome of patients with HCL or be more cost-effective.

Several groups have demonstrated that rituximab following treatment with purine analogs can eradicate MRD [18,19]. However, these studies have short follow-up durations, include a small number of patients, use different definitions of CR and MRD, and assess MRD at different time points following treatment with cladribine. Therefore, the clinical value of MRD eradication in patients who achieve CR by conventional criteria remains to be demonstrated, and future studies should attempt to define the population of patients with MRD+ HCL at high risk of relapse who may benefit from more aggressive initial therapeutic strategies.

Furthermore, with the advent of novel targeted therapies, the clinical significance of MRD should be reevaluated. The recent remarkable discovery of *BRAF*V600E mutation in over 90% of patients with HCL [20–22] provides a strong rationale for therapies targeting the mitogen activated protein (MAP) kinase signaling pathway and another MRD assessment tool using quantitative real-time polymerase chain reaction (RT-PCR) [22] or IHC with *BRAF*V600E mutation-specific antibody [23]. The selective mutant BRAF inhibitor, vemurafenib, has already been demonstrated to induce a rapid CR in heavily pretreated

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patients with refractory HCL [24,25], and the current ongoing clinical trials of vemurafenib in relapsed patients with HCL in Italy and the United States (NCT01711632) will provide more comprehensive information on rates and kinetics of MRD elimination and their impact on remission duration.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

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