How important is it to eradicate minimal residual disease in indolent non-Hodgkin’s lymphoma?

In Follicular non Hodgkin’s Lymphoma (FL-NHL) the molecular diagnosis and monitoring of the chimeric BCL2/IgH gene generated by the t(14;18) is an important tool in the diagnostic work-up at diagnosis and during the clinical follow-up. Although the clinical significance of circulating BCL2/IgH+ cells is still controversial, the persistence of these cells after conventional or high dose chemotherapy programs correlates with a shorter clinical remission. Quantitative PCR assays have been developed, which provide a reliable tool for the accurate evaluation of BCL2/IgH+ cells in the BM or peripheral blood (PB) and allow a better molecular monitoring of minimal residual disease after different therapeutic protocols. We have recently shown that the quantitative evaluation of the BCL2/IgH chimeric gene performed at diagnosis in the BM and PB can provide useful information as surrogate marker of the clinical outcome of FL-NHL patients. The clearance of neoplastic cells from BM and PB obtained either after conventional chemotherapy or after passive immunotherapy using the anti-CD20 chimeric monoclonal antibody Rituximab, can be accurately quantified. In our experience, an anthracycline containing regimen like CHOP and Rituximab are both able to remove approximately 2 logs of tumor infiltration thus explaining why patients with a limited lymphoma infiltration (1 positive cell in 10^5 normal cell or less) can achieve a molecular remission after CHOP chemotherapy alone. On the other hand, patients showing at diagnosis intermediate or high levels of BM and PB infiltration, benefit from the addition of Rituximab since they achieve a molecular CR in more than 70% of patients. We also confirm the notion that achieving the combined end point of clinical and molecular remission is one of the major goals in the therapy of FL-NHL. Indeed, no matter whether after CHOP alone or after sequential CHOP and Rituximab, patients in complete clinical and molecular remission show a significantly longer freedom from disease recurrence. In keeping with our results, several investigators have recently provided evidence on the value of RQ-PCR analysis in patients undergoing autologous hematopoietic stem cell transplantation. Laedtto and co-workers showed that the evaluation of tumor burden by RQ-PCR in stem cell harvest can predict the effectiveness of ex vivo purging after high dose chemotherapy. Along the same line, it has been shown that the ability of Rituximab to eradicate contaminating tumor cells in the graft can contribute to improve the clinical outcome of autologous transplantation. Moreover, the tumor load of BCL2/IgH+ cells detected in BM or PB samples post-autologous or allogeneic transplantation in FL-NHL was also found to positively correlate with the duration of clinical remission. In addition, our results further support the notion that Rituximab should be promptly offered to all patients who fail to achieve a complete clinical and molecular response at the end of front line therapy. Moreover, the quantitative PCR analysis performed at diagnosis may help in defining patients eligible for studies using high dose chemotherapy as initial treatment. In conclusion, our results support the clinical value of a quantitative evaluation of BCL2/IgH+ cells at diagnosis, which may help to define the probability of response to conventional chemotherapy with or without the addition of Rituximab. Our data also confirm that molecular monitoring of minimal residual disease allows an early identification of patients with a remarkably higher risk of disease recurrence.

References

3. Price CG, Meerbux J, Murtagh S, et al. The significance of circulating cells carrying t(14;18) in long