

## Chronic Lymphocytic Leukemia below the Radar

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Chronic Lymphocytic Leukemia (CLL) has therefore recently stated that a new era is born for this entity. The first new compounds which will be shortly approved will be the anti-CD20 antibody obinutuzumab, the oral bruton tyrosine kinase inhibitor ibrutinib and the oral phosphoinositide-3-kinase inhibitor idelalisib[1]. However, a substantial number of additional agents with identical or different therapeutic targets are currently under clinical investigation and one cannot yet overview the numerous options which will be conceivable regarding any combination of those.

All these new approaches have in common that they frequently produce therapy responses which lie clearly below clinical or conventional hematological detection limits. Thus, to precisely assess the remaining disease burden more sensitive techniques such as multiparameter flow cytometry or molecular genetics have to be applied[2]. While flow cytometry is broadly available its detection limit is usually in the range of  $1 \times 10^4$ . Real-time quantitative Polymerase Chain Reaction (qPCR) is more sensitive for detecting Minimal Residual Disease (MRD) below that level but is restricted to few highly specialised laboratories.

But do we really need this information? Isn't CLL mostly a rather indolent disease which can be sufficiently be treated once it pops up again onto the radar after a period of low-level flying?

I think, these questions should be answered differentially depending on individual patient and disease characteristics. Certainly, MRD detection is of no established value in early disease stages where no treatment is indicated. So far no data exist showing that a given extend of monoclonal B lymphocytosis (MBL) or a defined amount of CLL

cells predicts a progressive disease[3]. And the exact significance of established prognostic markers like molecular cytogenetics during early disease stages remains to be determined. Also, in most cases of manifest CLL with favourable prognostic factors (e.g. del(13q) or hypermutated immunoglobulin variable heavy chain, IgVH) disease monitoring by flow cytometry or molecular genetics is likely to be irrelevant. However, in the context with newer therapies it could be shown that remission depth has a significant impact on prognosis. Moreover, early detection of MRD may be of particular importance in high risk patients who underwent allogeneic stem cell transplantation[4].

Taken together, the new therapeutic era in CLL also challenges our diagnostic tools and requires their validation in an altered clinical setting.

### References

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