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The role of minimal residual disease elimination in the outcome of chronic lymphocytic leukemia

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There have been significant changes during the past few decades in the management of chronic lymphocytic leukemia (CLL), a disease with a very heterogeneous outcome ranging from survival for decades, without evidence of progression, to rapid transformation into more aggressive disease and early death.¹

An increasing awareness of the prognostic factors and molecular heterogeneity of CLL has helped to identify distinct risk categories, enabling early identification of patients likely to develop more aggressive disease. In addition, newer treatment agents and strategies, including monoclonal antibodies and hematopoietic stem cell transplantation (SCT), have resulted in much higher complete response (CR) rates than seen previously with conventional therapy.

These newer therapeutic strategies include combination chemotherapy with monoclonal antibodies. This approach is discussed by Engert on pages 23–28 of this supplement, and a recent retrospective analysis showed that fludarabine combined with alemtuzumab (FluCam) is more effective than either agent alone, most probably due to the synergistic action of the two agents.^{2,3} Further studies are underway, including a phase III trial comparing FluCam with standard fludarabine monotherapy and a phase II trial investigating the combination of cyclophosphamide with FluCam. With regard to the application of SCT in CLL, the relative roles of autologous and allogeneic SCT are reviewed by Ritgen *et al.* in their article on the elimination of minimal residual disease (MRD) in CLL by SCT (pages 9–11 of this supplement), including the reduction of graft-versus-host-disease (GVHD) by alemtuzumab without compromising efficacy in non-myeloablative allogeneic SCT.⁴

The accurate monitoring of residual disease has become more significant as the management of CLL has begun to shift away from a palliative approach towards more durable remissions and a potential cure for CLL. In an article on MRD evaluation in CLL (pages 5–8 of this supplement), Ritgen *et al.* have

reviewed the different methods available for monitoring MRD, including polymerase chain reaction (PCR) techniques, such as consensus PCR, *real-time* PCR (RQ-PCR) and flow cytometry, particularly the MRD flow assay.⁵ Several studies have correlated eventual relapse with the persistence of MRD.^{5–7} However, achieving an MRD-negative status does not necessarily imply a cure, even when stringent criteria are used to assess MRD, as disease may eventually reappear.^{5,8} Since alemtuzumab is more effective against peripheral blood CLL cells than against nodal disease or extranodal tumors, it has been suggested that alemtuzumab may be particularly effective in eradicating MRD.^{9,10} As reviewed by O'Brien on pages 18–22 of this supplement, alemtuzumab can further reduce MRD in patients already in clinical remission and effectively induce molecular remission. Alemtuzumab is a highly effective method for purging MRD following chemotherapy induction, without compromising subsequent stem cell mobilization so that patients can proceed to SCT.

The role of alemtuzumab in eliminating MRD negativity is discussed further by Hillmen on pages 12–17 of this supplement. Results from Moreton *et al.*¹¹ have clearly demonstrated that it is possible to achieve MRD negative remission in patients of all ages with refractory disease, with the overall survival for patients with MRD-negative remission being 84% at 5 years.

Discussion

The Expert Panel of the Workshop took part with delegates in a discussion of key questions concerning the elimination of MRD in the outcome of CLL. These questions were:

- Should MRD elimination be integrated into CLL response criteria?
- What is the method of choice for measuring MRD negativity?
- In which patient population is MRD negativity a major goal?
- What is the role of transplantation versus chemoimmunotherapy in MRD elimination in CLL?

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The Expert Workshop concluded with a summary of the main issues.

Should MRD elimination be integrated into CLL response criteria?

MRD eradication is an important target in the treatment of CLL because MRD negativity is clearly correlated with improved outcome. However, MRD assessment currently applies to a small minority of patients. Until more data are available, MRD cannot be recommended as a surrogate marker of treatment efficacy for general clinical application. Whenever possible, MRD assessment should be included in the response criteria of future clinical trials.

In principle, MRD negativity can be used to tailor treatment for individual patients, but it remains unproven whether the achievement of MRD negativity will also achieve cure of CLL. Clinical trials are needed to follow-up MRD status and to test whether different modalities of achieving MRD negativity will provide a cure.

The biology of CLL may change with therapy. Treating CLL patients too early may disturb their disease homeostasis and select more aggressive leukemic clones. This might result in the disease progressing sooner than it might have otherwise done, so that patients fail faster with treatment than without treatment. As yet, no clear benefit has been shown to support the early treatment of CLL in preference to a *watch and wait* policy. Several trials are currently planned or ongoing to assess whether early and aggressive therapy will improve the outcome of CLL.

What is the method of choice for measuring MRD negativity?

With regard to selection of the method for measuring MRD negativity, blood sampling is sufficient in the majority of patients. When taking a bone marrow sample, it should be remembered that the first draught of bone marrow cells will provide the most accurate result. Although four-color flow cytometry is slightly less sensitive than PCR in measuring MRD negativity, it is easier to perform. It was therefore recommended that four-color flow cytometry should be used to measure MRD negativity. Only when the result is negative should allele-specific oligonucleotide (ASO)-PCR be performed. It was emphasized that research publications should state the sensitivity of the method used to measure MRD negativity, as this will affect the interpretation of results and comparison between trials.

In which patient population is MRD negativity a major goal?

Currently, MRD negativity is a major goal only for patients treated in clinical trials. Within clinical trials,

MRD negativity is likely to apply to younger, physically fit patients because they are usually treated with more intensive regimens (e.g. chemoimmunotherapy or transplantation) which have the goal of eradicating tumor cells.

What is the role of transplantation versus chemoimmunotherapy in MRD elimination in CLL?

Autologous SCT is no longer the only way to achieve MRD negativity in patients with CLL. Chemoimmunotherapy is becoming increasingly potent and is able to achieve the same quality of remission as assessed by PCR. It is not possible to compare allogeneic SCT with chemoimmunotherapy because of the much higher mortality rate associated with allogeneic SCT.

Conclusions

The advent of novel therapeutic approaches in CLL has allowed the goal of achieving MRD-negative complete responses to become a possibility. Disease progression is inevitable in patients who are MRD-positive whereas MRD-negative patients are able to attain durable remissions. Alemtuzumab has been proven to be effective in refractory disease, as first-line therapy and in combination therapy with chemotherapeutic agents including fludarabine (FluCam). Alemtuzumab also has a proven role in eradicating MRD following chemotherapy induction and in preventing GVHD in non-myeloablative allogeneic chemotherapy.

Until further data are available, MRD negativity is not recommended for general clinical application as a surrogate measure of treatment efficacy. However, a systematic assessment of MRD should be part of the response criteria within all future clinical trials using chemoimmunotherapy.

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