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Guideline on the use of minimal residue disease as an endpoint in chronic lymphocytic leukaemia studies

Draft

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30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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Executive summary

Minimal residual disease (MRD) negativity in patients in clinical complete remission (= MRD response rate) after induction therapy may be used as an intermediate endpoint for licensure in randomised well controlled studies designed to show superiority in terms of PFS. This requires that the benefit/risk of the experimental regimen is well characterised in CLL and that these data would support the superiority of the regimen over established regimens used as induction therapy in CLL.

1. Introduction (background)

Chronic lymphocytic leukaemia (CLL) is the most common leukaemia in the Western world with an incidence of 4.2/100000/year that increases to >30/100000/year at an age >80 years.

Treatment is recommended only for those patients with active, symptomatic disease. With the introduction of new immune-chemotherapeutic combinations over the last decade the efficacy of treating patients with CLL has greatly improved and median PFS now ranges from 3.5 to 6.7 years after first line therapy whilst median OS for patients with advanced stages (Binet C or Rai IV) is approximately 6.5 years. Allogeneic stem cell transplant remains the only curative therapy and it is recommended for patients with very high risk and/or refractory disease.

Because patients achieving clinical complete remission (CR) according to international guidelines will eventually relapse, minimal residual disease (MRD) undetectable at clinical and morphological level must have been present. Therefore, the quality of CR should be also assessed for the absence of MRD. The vast improvement in MRD detection over the last two decades has now led to the concept that low MRD levels are a desirable and achievable goal of CLL therapy.

The scope of this document is to describe the basis and regulatory requirements for the use of MRD as an intermediate endpoint to predict clinical benefit in trials in CLL. At present, this guidance is not applicable to other clinical settings.

2. Scope

MRD

Definition & threshold

MRD is an objective measure of disease status defined by the number of leukaemic cells remaining in peripheral blood or bone marrow following treatment. According to current international definitions MRD negativity equals a quantitative detection of less than 1 CLL cell in 10000 leukocytes (MRD level $< 10^{-4}$).

There is no data currently available to support a MRD level below the 10^{-4} threshold would provide added clinical benefit.

Laboratory assays

Although MRD evaluation is still not widely standardized there are currently two analytical methods capable of assessing MRD status at the required threshold. There is no specific recommendation on the method to be used as both are considered appropriate.

A quality management system that includes the laboratory(s) organisational structure, responsibilities, policies and standards needed to ensure accuracy and satisfactory quality of the MRD evaluation assay

would be required. The use of central laboratories is not considered a regulatory requirement provided a robust quality system is in place.

- Real-time quantitative PCR (RQ-PCR)

Every leukaemic B-cell clone carries a unique IGHV-IGHD-IGHJ rearrangement that can be amplified by PCR using primers. Allele specific oligonucleotide immunoglobulin heavy chain real-time quantitative PCR (ASO IGH RQ-PCR) is labour intensive as it requires the sequencing of each clone-specific rearrangement but has sensitivity in the range of 10^{-4} to 10^{-5}.

Limitations of the method apply in case of changes in phenotype between baseline and follow up investigations. Since specific primers address a single rearranged IgH gene sequence, there is a certain risk of target gene loss due to ongoing rearrangements in the IgH region which would result in reduced sensitivity. In order to minimize false negative MRD measurements, two Ig PCR targets should be used if oligoclonal clones are found at the time of diagnosis.

A major advantage is that the samples do not need to be fresh and can be shipped to a single centre for analysis. Conserved samples could further enable retrospective analysis in clinical trials. In addition, ASO RQ-PCR offers a higher qualitative sensitivity below the threshold of 10^{-4} which might be relevant in clinical trials exploring complete eradication of the disease.

- Four-colour or more flow cytometry

Because CLL cells show a characteristic unique phenotype, low amount of leukaemic cells can be detected using flow cytometry to the required sensitivity level of 10^{-4}. The sensitivity of MRD flow primarily depends on the availability of sufficient numbers of leukocytes in a sample.

The main advantage of this method is that it is simpler and faster as it does not require the design of clone-specific primers. It uses a widely available technology and is therefore a broadly applicable method. A disadvantage is that samples are required to be fresh (48h). Appropriate handling and transport to central laboratories may be difficult to establish in multi-centre, multi-national clinical trials.

Samples

MRD status can be assessed either from peripheral blood (PB) or bone marrow (BM).

It is recommended that for all medicinal products irrespective of drug class, patients are screened for CLL eradication in PB first. If MRD negativity is shown, this should be confirmed in the BM.

Utility

It is accepted that in case of disease progression, response to therapy is the most important prognostic factor for survival. A profound reduction of tumour load and not the treatment regimen by which this reduction is induced is the key factor for durable remission.

The availability of MRD data shortly after treatment is important because with more effective treatment regimens PFS will only be evaluable after a long observation period.

Available data has shown that MRD negativity at the end of induction treatment is a strong predictor of PFS and OS irrespective of the following:

- Type and line of treatment

  Although patients are more likely to reach MRD negativity with some therapies compared to others, for those patients that achieved MRD negativity by different therapies there appear to be no differences in terms of PFS or OS. Data are still limited, however.

- Known poor pre-treatment risk factors (e.g. deletion chromosomes 11q and 17p, mutated TP53, un-mutated IGHV status, ZAP-70 expression)

Current evidence suggests that in unselected patient cohorts an MRD level ≥ 10^{-4} is associated to a median PFS of about 2 years, whereas a MRD level < 10^{-4} predicts a median PFS of around 6 years.

The validation of MRD negativity as a surrogate endpoint requires that the treatment effect on this marker can explain quantitatively the treatment effect in terms of PFS. This remains to be shown. Qualitatively available data are sufficiently convincing for MDR negativity to be used as an intermediate endpoint in randomised controlled trials.

MRD as endpoint for licensure

A difference in MRD response rates can be used as primary evidence of clinical benefit to obtain early licensure in randomised CLL trials designed to show superiority in terms of PFS provided all the following conditions are met:

Study design and results

- The difference in MRD response rate between study arms is large enough to predict that a relevant PFS benefit will appear on mature data
- PFS confirmation will be obtained at a further analysis with the trial being prospectively powered for this purpose.
- The statistical analysis of MRD will have been pre-planned as well and the statistical analysis plan should clearly describe how MRD and PFS are assessed.
- In case of early approval based on MRD response rate, an analysis of PFS would be required from the holder of the marketing authorisation in an agreed timeframe.
- All patients should be followed for OS
- All patients with clinical CR should be assessed for MRD
- The control regimen is selected according to the criteria set out in the main anticancer guideline.

MRD definitions and method

- MRD status should be measured by a standardised method with a quantitative lower limit of at least < 10-4
- A quality control scheme for all laboratories providing CLL MRD analysis will be required
- Measurement of MRD should be conducted at end-of-treatment response final staging assessment (around 3 months after end of treatment) to fully represent the effect of treatment.
- MRD status will be considered negative if the proportion of malignant cells is < 10-4
- MRD response rate is defined as the proportion of patients in the ITT population in whom a clinical complete response (CR) and MRD negative status is achieved following induction treatment in CLL.
- Patients who achieve clinical CR and MRD negative status at the end of treatment will be counted as MRD responders
- Patients with missing MRD assessment and with MRD-positive status will be counted as MRD non-responders.

Additional recommendations and considerations

- Exploratory analyses are recommended using different cut-offs for “MRD negativity” in patients with CR as well as PR. The prognostic value of different levels of MRD may also be explored
- For exploratory purposes, it is recommended that all patients responding to therapy (including PR) should have their MRD status assessed at least in peripheral blood.
- For patients that undergo allogeneic SCT, early MRD positivity is common probably due to the fact the onset of graft-versus-leukaemia is not immediate. MRD negativity can be achieved several months after allogeneic SCT.

Additional areas of uncertainty

It has been suggested that the kinetics of MRD rather than a single MRD assessment may be more meaningful because it is the increase of MRD over time and not only its persistence that is eventually followed by clinical relapse. The kinetics of relapse is exponential even at the lowest evaluable levels of the disease.

At present it is not known whether long term outcome can be improved if MRD assessment is used to guide therapy, either to improve the quality of response through consolidation therapy or to prevent relapse by therapies based on reappearance of MRD.

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