Leukaemia Care
YOUR Blood Cancer Charity

Advocacy toolkit

Minimal Residual Disease (MRD)

After a leukaemia diagnosis there are many acronyms that you will come across and MRD is likely to be one of them. In this toolkit, we look at what minimal residual disease (MRD) means and why it is significant.

What is MRD?

Minimal residual disease is the presence of small, but measurable, numbers of leukaemia cells in the blood of a patient who does not have any clinical presentation of a blood cancer (i.e. the patient is in remission).

Morphological remission vs Molecular remission

The current definition of remission refers to morphological remission. This means that there is no physical evidence of leukaemia. In particular:

- Normal blood count
- Normal development of blood cells in the bone marrow
- Blast count is less than 5% - every person will have a certain number of immature white blood cells (blasts). Under the microscope it is difficult to distinguish these from cancerous immature white cells, therefore the <5% threshold is used to define normal bone marrow.

However, just because there are no visible signs of leukaemia there can still be small numbers of leukaemia cells hidden within the blood and this is Minimal Residual Disease.

Molecular remission, on the other hand, is the absence of both morphological signs of leukaemia and MRD (or MRD negativity). To determine MRD negativity in this instance, the most sensitive of laboratory techniques (PCR) must be used, which you can find out more about below.

MRD Positive vs MRD Negative

MRD Positivity

The current threshold for a positive MRD status is the presence of 1 or more leukaemia cell out of every 10,000 healthy cells. This equates to at least 0.01% of all cells being leukaemic.

MRD Negativity
This means that there are no detectable leukaemia cells – as far as can be seen using current laboratory techniques.

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FACT: The first major breakthrough in developing techniques to detect MRD was in 1980. Since this time, a number of developments have been made and research suggests we can now detect just 1 leukaemic cell out of 1 million blood cells (0.0001%) using the very latest techniques.

How is MRD measured?

There are different methods of detecting MRD and the preferred method depends on the type of leukaemia and the underlying genetic mutations that are causing it.

For example, flow cytometry and Next Generation Sequencing (NGS) are the preferred methods used for detecting MRD in B-cell leukaemias, such as CLL.

On the other hand, PCR is the preferred method of detecting MRD in leukaemias with a specific gene rearrangement. Such as, CML that has the BCR-ABL gene rearrangement, and some types of ALL and AML.

Flow Cytometry

Flow cytometry involves shining a beam of light at single blood cells and detecting:

1) The scattering of light – the direction that the light is scattered indicates both the size and internal complexity of the cell.

Or

2) The wavelength (colour) of fluorescence emitted– it is possible to tag certain cells (e.g. leukaemia cells) with a florescent colour if there is a known and unique site of attachment (marker) on the cell.

A particular wavelength of florescent light will be emitted when the light beam shines on the cell and this indicates that a leukaemia cell, for example, has been detected.

Flow cytometry is sensitive enough to detect 1 leukaemia cell in 10,000 cells (0.01%) and is the most commonly used method of MRD detection, hence why the MRD positive threshold is also 0.01%.

Advantages:

- Fast
- Normally available in laboratories

Disadvantages:

-Samples need to be taken and analysed within 48hours
-Not as sensitive as other techniques
-Need to have extensive knowledge to select the best markers and analyse the result profiles

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Next Generation Sequencing (NGS)

NGS refers to all techniques that can sequence DNA quickly, in some cases a full human genome (i.e. a map off all genes) can be sequenced within a day.
In the 1990s it took numerous international teams of scientists 10 years to map the very first human genome .

While this method is not ordinarily used, research is identifying the benefits of using NGS to detect MRD. These include:

- The ability to detect leukaemia cells with different mutations – avoiding issues with missed sub-populations of leukaemia cells.
- Quicker, as there is no need to develop patient-specific tools.
- Able to detect 1 leukaemia cell in 100,000 blood cells (0.001%), but some research has suggested this could be even more sensitive, detecting 1 leukaemia cell in 1 million blood cells (0.0001%).

Polymerase Chain Reaction (PCR)

PCR is the process of taking either a single copy, or small number of copies, of a DNA segment and copying it multiple times over to increase the amount (amplification). It is the technique that is used for identifying DNA within a crime scene, for example.

For the use of MRD detection, there must be a known genetic difference within the leukaemia cells. For example, Philadelphia positive leukaemia has a new gene, BCR-ABL, which is not found in healthy cells. This gene can then be targeted for amplification.

Using PCR enables the identification of 1 leukaemia cell in up to 100,000 blood cells (0.001%).

Advantages:

- MRD detection by PCR is both quality-controlled and standardised across 23 countries by EuroMRD. (http://www.euromrd.org/usr/pub/pub.php)

Disadvantages:

- Can take up-to two weeks to carry out, as it requires patient specific tools.
- Expensive and not always available in every hospital lab.
- The predominant gene mutation in the leukaemia cells can change over the course of treatment and therefore, there must be significant expertise to identify the best gene sequence to amplify. There may also be small numbers of leukaemia cells with different mutations (sub-populations) that will not be detected.

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What is the significance of MRD?

Clinicians and researchers are recognising the significance of MRD and this is leading to greater consideration on whether MRD negativity should be the therapeutic end point, as opposed to morphological remission.

1) ***Indicator of prognosis/outcome***

Analysing the MRD status of patients at different times along their treatment has proven to be a better indicator of prognosis and relapse.

-Patients who have an early response to treatment and achieve MRD negativity are seen to have a lower risk disease than those who respond late.
-Patients who are MRD negative at the end of a cycle of treatment are much less likely to relapse than those who are MRD positive.

2) ***Direct treatment decisions***

The prognostic impact of MRD status can then be used to influence the treatment decisions that are subsequently made.

-Additional actions could be taken to treat a patient who is MRD positive at the end of treatment. This may prevent a relapse and improve the patients overall outcome.
-The other option, which requires greater consideration from the clinical community, is the potential to give early responders a different, less intensive course of treatment. Preventing relapse but also avoiding side-effects of treatments.

What is the significance of MRD for specific leukaemia types?

Chronic Myeloid Leukaemia and MRD

The value of MRD has been massively recognised with discovery of tyrosine kinase inhibitor (TKI) drugs that target the genetic mutation driving the majority of CML cases.

The response to these drugs in treating the leukaemia is so impressive that the majority of patients will achieve MRD and in many cases this will be MRD negativity. This has become a crucial factor in recent years, as many patients who have been MRD negative for a long period of time are attempting to stop their drugs and observe whether they remain in remission.

In about 40% of patients, MRD negativity remains with the removal of the drugs. This is hugely significant as this is indicative of a potential cure.

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Acute Lymphoblastic Leukaemia and MRD

The most significant application of MRD in the treatment of ALL is assessing the MRD status of patients following chemotherapy treatment. In particular, if patients are MRD positive, studies have shown that stem cell transplant does not improve the prognosis of a patient. Therefore, it is questioned whether alternative treatment should be used to induce MRD negativity.

One treatment which has proven to be effective in inducing MRD negativity in refractory or relapsed patients with Philadelphia-negative ALL is blinatumomab. This is a type of immunotherapy, called a monoclonal antibody, which you can read more about in our immunotherapy toolkit.

In a pilot study of 21 patients, 80% of patients achieved MRD-negativity and only five patients went on to relapse .

In a larger trial, named TOWER, patients were recruited who had previously relapsed and had poor prognosis. 42% gained an MRD-negative status with blinatumomab compared with just 20% who received the current first choice of treatment. Additionally, the median survival was almost doubled .

Learn more about MRD and ALL in this presentation from the Leukaemia and Lymphoma Society: https://www.lls.org/patient-education-webcasts/the-impact-of-minimal-residual-disease-in-acute-lymphoblastic-leukemia

Acute Myeloid Leukaemia and MRD

There has been a growing amount of evidence into the prognostic value of MRD status in AML patients in recent years. There is, however, a huge challenge in widely implementing MRD testing for AML and this is due to the large number of different mutations that can be driving the leukaemia. This is known as the molecular heterogeneity.

It has been estimated that in each individual case of AML there are at least 10 different mutations present in the leukaemic cells. Additionally, the mutations could be found in any of 200 genes, which have been identified as commonly implicated in AML. Therefore, MRD status testing on AML patients is required to be patient-specific, and while feasible with current technologies, this is hard to implement widely due to the cost involved.

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Chronic Lymphocytic Leukaemia and MRD

While there is much evidence for the prognostic and survival impact of MRD-negativity following chemoimmunotherapy, a recent review suggests that its value alongside the use of more novel treatments for CLL requires significantly more research .

One example of a novel treatment for CLL is venetoclax in the treatment of CLL with a particular gene deletion. A clinical trial saw 30% of patients, with relapsed or refractory CLL, achieve MRD-negativity and many achieved 24-months progression free survival.

Further questions

If you have any further questions about Minimal Residual Disease (MRD) then you can contact our Campaigns and Advocacy team. They are available Monday to Friday from 9:00am – 5:30pm.

If you would like to speak to them, you can:
- Call our office line on 01905 755977
- Send them an email at advocacy@leukaemiacare.org.uk
- You can also call the help line, free of charge on 08088 010 444. The team will pass your enquiry onto the Campaigns and Advocacy team.

Please note that our Campaigns and Advocacy team are unable to provide:
- Detailed medical advice or recommendations
- Legal advice
- Advocacy for a course of action which is contrary to the aims and objectives of Leukaemia Care.