Response evaluation and long-term follow-up

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**introduction**

The assessment of response after treatment is important for several reasons. In case of response, it provides arguments to continue the treatment. It makes it for the patient easier to accept potential side-effects. In the absence of a response, it is not necessary to harm the patient anymore and, if there is a choice for alternative treatment, it may help to facilitate this decision. Response assessment is also important to compare the results from various clinical trials. Generally, the tests abnormal at the time of diagnosis are repeated to demonstrate response.

At the time of diagnosis, many patients have \(10^{11} - 10^{12}\) tumor cells in their body. From this it is clear that to result in cure, 11- to 12-log tumor cell kill is necessary.

Even the most sensitive technique, however, is only able to find one tumor cell within \(10^{4} - 10^{6}\) normal cells, so this means that the threshold to demonstrate of tumor cells is somewhere one cell in \(10^{24} / C \) cells. To achieve this threshold, not only 6-log tumor cell kill is necessary but also \(10^{6}\) tumor cells can still be present. This sensitivity can only be reached using molecular techniques. In more routine procedures, demonstration of a complete response (CR) means that somewhere \(10^{9}\) tumor cells may be left. When restaging patients, one should always keep this in mind and realize that complete remission only means that no tumor cells can be demonstrated and that complete remission is not identical with cure.

Historically, different definitions are used for the various hematological malignancies. These will be discussed in the next sections on the various diseases.

The situation in which it is most likely that viable tumor cells are present but cannot be demonstrated as just explained is called minimal residual disease.

**general response criteria**

**acute leukemias**

Historically, the remission status of patients with acute leukemia is defined by the presence of blastic cells. To achieve complete remission, patients should have <5% of leukemic blasts in their marrow smear and at the same time a fully recovered peripheral blood. It is clear from this definition that many tumor cells can be present, although the patient, according to the definition, may have a CR.

To make the definition of CR more sensitive, additional techniques can be included such as cytogenetics. This is only the case if the results are abnormal at the time of response assessment (in patients with cytogenetic abnormalities at the time of diagnosis, all cytogenetic abnormalities should have disappeared at the time of response assessment). This may make the assessment of a CR more reliable. Clinical studies, however, are generally still based on the morphological definition of <5% blasts in the marrow smear.

The introduction of molecular techniques makes the assessment of response in patients with molecularly identifiable abnormalities even more sensitive. In some situations even one in \(10^{4} - 10^{6}\) normal cells can be found. From recent reports, however, it is clear that not all patients with molecularly identifiable abnormalities necessarily do relapse. On the other hand, patients with a molecular CR are less likely to relapse.

In patients with t(15;17) abnormality, the assessment of the product of this translocation (pml/rar alpha) is very sensitive and the increase of this product in peripheral blood signifies that the relapse is imminent.

The measurement of bcr-abl product in patients with Philadelphia chromosome-positive acute lymphoblastic leukemia is a very sensitive technique which can reliably assess CR rate and imminent relapse.

ESMO has defined the following follow-up guidelines:

- Patients are followed clinically with hematological examination to detect early relapse.
- Serial bone marrow examination is of uncertain value in patients under remission without any clinical or hematological evidence of relapse.

**myelodysplastic syndrome**

The assessment of response in patients with myelodysplastic syndrome (MDS) is only important when the patient gets active treatment. If the choice has been made for supportive care, only those parameters should be followed which influence the decisions for transfusion or the treatment of infection.

A subset of patients with MDS is treated with chemotherapy. For these patients, generally, the same criteria are followed to assess response as in patients with acute leukemia.

Those patients treated with growth factor support parameters should be followed, which assesses the efficacy of the growth factor.

**chronic lymphocytic leukemia**

There are no clear response criteria for chronic lymphocytic leukemia. CRs are hardly ever achieved, but may be defined as...
the absence of malignance cells and a full recovery of peripheral blood. Generally, the treatment is palliative and response assessment can be made by a normalization of the abnormal blood values.

ESMO has defined the following follow-up guidelines:

• Follow-up of asymptomatic patients should include a blood cell count every 3 months, as well as a regular examination of lymph nodes, liver, and spleen.

• Special attention should be given to the number of atypical lymphocytes, in particular to prolymphocytes.

**malignant lymphomas**

In patients with Hodgkin’s disease or non-Hodgkin’s lymphoma (NHL), restaging during and after therapy is very important. Strict criteria for CR, complete response unconfirmed (CRu), partial response (PR), etc., have been defined (see Table 1). In malignant lymphoma, one has to realize that lymph nodes sites <1.5 cm may also have microscopical disease in apparently normal lymph nodes. Positron emission tomography (PET) scanning may be helpful in selected cases such as bulk and PR. In the near future, new response criteria [including the use of PET–computed tomography (CT) scanning] will be introduced. Using this technology, most likely, the group of CRu will disappear.

ESMO has defined the following follow-up guidelines for follicular NHL:

• History and physical examination every 3 months for 2 years, every 6 months for three additional years, and subsequently once a year with special attention to transformation and secondary malignancies including secondary leukemia.

• Blood count at 3, 6, 12, and 24 months, then only as needed for evaluation of suspicious symptoms.

• Evaluation of thyroid function in patients with irradiation to the neck at 1, 2, and 5 years.

• Minimal adequate radiological or ultrasound examinations at 6, 12, and 24 months after end of treatment.

ESMO has defined the following follow-up guidelines for newly diagnosed large-cell NHL:

• History and physical examination every 3 months for 2 years, every 6 months for three more years, and then once a year with attention to development of secondary tumors.

• High-risk patients still with curative options, such as high-dose chemotherapy with stem-cell support, may mandate more frequent controls.

• Blood count and lactate dehydrogenase at 3, 6, 12, and 24 months, then only as needed for evaluation of suspicious symptoms or clinical findings in those patients suitable for further therapy.

• Evaluation of thyroid dysfunction [thyroid-stimulating hormone (TSH)] in patients with irradiation to the neck at 1, 2, and at least at 5 years.

• After having received chest irradiation at premenopausal age, especially at an age <25 years, women should be screened for secondary breast cancers clinically and, after the age of 40–50 years, by mammography.

• Minimal adequate radiological examinations at 6, 12, and 24 months after end of treatment, by CT scan when indicated by site of disease.

ESMO has defined the following follow-up guidelines for relapsed large-cell NHL:

• History and physical examination every 3 months for 2 years, every 6 months for three more years, and then once a year with attention to development of secondary tumors.

• Full blood count at 3, 6, 12, and 24 months, then only as needed for evaluation of suspicious symptoms or clinical findings in those patients suitable for further therapy.

• Evaluation of thyroid function (TSH) in patients with irradiation to the neck at 1, 2, and 5 years.

• After having received chest irradiation at premenopausal age, especially at an age <25 years, women should be screened for secondary breast cancers clinically and, after the age of 40–50 years, by mammography.

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**Table 1.** Response criteria for malignant lymphoma

<table>
<thead>
<tr>
<th>Response</th>
<th>Criteria</th>
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<tbody>
<tr>
<td><strong>CR</strong></td>
<td>Complete disappearance of all detectable clinical and radiographic evidence of disease. Disappearance of all disease-related symptoms if present before therapy. Normal lactate dehydrogenase (i.e. ≤ ULN). All nodes and nodal masses must have reduced in size to ≤1.0 cm or If some nodes have regressed to a size between 1.0 and 1.5 cm the SPD of the indicator lesions must have regressed by &gt;75%. If the bone marrow was involved by lymphoma before treatment, the infiltrate must be cleared on repeat bone marrow aspirate and biopsy of the same site.</td>
</tr>
<tr>
<td><strong>CR/CRu</strong></td>
<td>A residual lymph node mass &gt;1.5 cm in greatest transverse diameter that has regressed by &gt;75% in the PPD size. Individual nodes that were previously confluent must have regressed by &gt;75% in their SPD size compared with the size of the original mass. The SPD size of the indicator lesions must have regressed with &gt;75%. Indeterminate bone marrow (increased number or size of aggregates without cytologic or architectural atypia).</td>
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<tr>
<td><strong>PR</strong></td>
<td>50% decrease in SPD of the indicator lesions. 50% decrease in SPD of splenic and hepatic nodules if present and bidimensionally measurable at start of treatment. No increase in the size of any single node, nodule, liver, or spleen by &gt;25%.</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>Less than a PR but is not progressive disease.</td>
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<tr>
<td><strong>PD</strong></td>
<td>≥50% increase in the PPD size of any at baseline identified abnormal node, nodal mass or nodule. Appearance of any new lesion during or at the end of therapy.</td>
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</table>

CR, complete response; CRu, complete response unconfirmed; PR, partial response; SD, stable disease; and PD, partial disease; ULN, upper limits of normal.
Patients are followed by blood cell counts once weekly during abnormalities other than the Philadelphia chromosome. Announced by occurrence of additional cytogenetic it will disappear completely. A decrease of the cytogenetic abnormality. In a subset of patients, can be followed using cytogenetics. Imatinib therapy results in after the start of treatment. In addition, the disease activity and should show a 3-log decrease in the first 12–24 months intervals the bcr-abl product in the blood should be measured chronic myeloid leukemia. This means that with regular that a rapid molecular response may be of value in patients with chronic myeloid leukemia and myeloproliferative diseases. Chronic myeloid leukemia

In patients with chronic myeloid leukemia, response assessment is very important. This has to do with the increasing knowledge that a rapid molecular response may be of value in patients with chronic myeloid leukemia. This means that with regular intervals the bcr-abl product in the blood should be measured and should show a 3-log decrease in the first 12–24 months after the start of treatment. In addition, the disease activity can be followed using cytogenetics. Imatinib therapy results in a decrease of the cytogenetic abnormality. In a subset of patients, it will disappear completely.

Acceleration in patients with chronic myeloid leukemia, or even the transformation to a blast crisis, is frequently announced by occurrence of additional cytogenetic abnormalities other than the Philadelphia chromosome.

ESMO has defined the following follow-up guidelines:

- Patients are followed by blood cell counts once weekly during the first weeks of therapy and every 1–2 months later on. Bone marrow cytogenetics (and/or quantitative PCR of bcr-abl) should be carried out in imatinib-treated or interferon-treated patients every 6 months.
- Patients relapsing after allotransplant may still have curative options, e.g., donor lymphocyte transfusions, and require more frequent controls.

Polycytemia vera and essential thrombocytosis

Patients with polycytemia vera and essential thrombocytosis should be followed using standard hemaglobin. A normalization of hematocrit or platelets is what should be achieved for.

There is no proven efficacy for the follow-up of other parameters. Patients with myelofibrosis would also be followed assessing their abnormal blood values, if one tries to normalize these with therapy.

**Long-term follow-up**

In contrast to short-term follow-up (mainly aiming for the detection for treatable relapses) the long-term follow-up is of importance to detect the long-term sequelae of the therapy, such as secondary malignancies, cardiac insufficiency, hormonal deregulations, and psychosocial complications.

The long-term follow-up is not disease specific. This issue, however, is only of relevance in diseases with sufficiently long survival.

The single most important situation is the long-term complications in Hodgkin’s disease. It is now recognized that

### Table 2. Evaluation of response in multiple myeloma (derived from ebmt/ibmtr/asbmt criteria)

<table>
<thead>
<tr>
<th>CR requires all of the following</th>
<th>Relapse, if after CR</th>
</tr>
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<tbody>
<tr>
<td>Immunofixation serum is negative</td>
<td>Serum M-protein &gt;0 or positive immunofixation serum</td>
</tr>
<tr>
<td>Immunofixation urine is negative</td>
<td>Urine M-protein &gt;0 or positive immunofixation urine</td>
</tr>
<tr>
<td>Plasma cells in bone marrow &lt;5%</td>
<td>Plasma cells in bone marrow &lt;5%</td>
</tr>
<tr>
<td>No increase in skeletal lesions</td>
<td>Plasmacytoma presence</td>
</tr>
<tr>
<td>Disappearance of soft tissue plasmacytoma</td>
<td>Increase in skeletal lesions compared with last known value</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>Hypercalcemia presence</td>
</tr>
</tbody>
</table>

CR, complete response; PR, partial response.
patients treated with combined modality therapy have an increased risk for MDS and acute leukemias. In addition, patients treated with mantle field irradiation have an increased likelihood to develop hypothyroidism, lung cancer, and breast cancer.

Patient with low-grade lymphoma and treated with high-dose therapy and autologous transplantation also appear to have an increased risk for MDS. Also years after (anthracyclin) containing chemotherapy, cardiac insufficiency may occur. This should be a consideration for long-term follow-up.