

Acute myeloblastic leukaemias and myelodysplastic syndromes in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

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incidence

The yearly incidence of the acute myeloblastic leukaemias (AMLs) in European adults is 5–8 cases per 100 000 individuals, and in myelodysplastic syndromes (MDSs) 4–5 new cases/100 000 are expected yearly. In individuals >60 years incidences of both AMLs and MDSs increase significantly, reaching 40–60 new cases of MDS per 100 000/year. Yearly mortality figures are 4–6 cases per 100 000 in AMLs and somewhat higher for MDSs.

diagnosis

The diagnosis of both AMLs and MDSs requires the examination of peripheral blood and bone marrow specimens. The work-up of these specimens should include morphology, cytochemistry, immunophenotyping (more important in AMLs than in MDSs), cytogenetics and molecular genetics.

Whilst historically classified by the largely descriptive French–American–British (FAB) criteria, myeloid neoplasms including MDSs and AMLs are now classified according to the WHO classification from 2001, revised in 2008. The WHO classification now incorporates, in addition to morphological criteria, genetics, immunophenotype data and clinical information into a diagnostic algorithm to delineate clinically significant disease entities. In the WHO classification the term ‘myeloid’ includes all cells belonging to the granulocytic, monocyte/macrophage, erythroid, megakaryocytic and mast cell lineages. The percentage of blast cells in the bone marrow is a practical tool for categorizing myeloid neoplasms into AML or MDS, respectively, where myeloid neoplasms with >20% blasts in the peripheral blood or bone marrow are considered

AMLs, either *de novo*, or having evolved from a pre-existing MDS. Blasts are defined using the criteria recently proposed by the International Working Group on Morphology of MDS. In contrast to a diagnosis of AML, MDSs remain a considerable diagnostic challenge, particularly in cases where blast counts are not increased in the bone marrow, and morphological findings are inconclusive. The ‘minimal’ diagnostic criteria for MDSs include the appropriate clinical setting, unequivocal dysplasia of ≥10% of cells from at least one myeloid lineage in the bone marrow, and causes of secondary dysplasia must be excluded. If morphological features are inconclusive, a diagnosis of MDS can still be made if one or several specific clonal chromosomal abnormalities are found on cytogenetics. In the absence of morphological and/or cytogenetic findings suggestive of MDS, flow cytometry abnormalities are not diagnostic of MDS. In uncertain cases, careful follow-up investigations (chiefly morphology and karyotyping) are recommended at regular intervals of at least several months.

risk assessment and prognostic factors

Patient age, initial leukocyte counts (in AMLs) and co-morbidity are important risk factors, but prognosis is chiefly governed by AML and MDS subtypes or entities. Morphology is still a particularly important tool to classify MDSs, defining such categories as the refractory anaemias with or without ring sideroblasts, or refractory cytopenia with multilineage dysplasia. AMLs having evolved from previously documented MDS generally have an adverse prognosis. Nowadays, molecular and genetic risk stratification have become the key principles to guide the therapy of both MDSs and AMLs.

karyotype/cytogenetics

AMLs with the chromosomal translocations t(15;17)(q22;q12), i.e. acute promyelocytic leukaemia (APL), t(8;21)(q22;q22), and inv(16)(p13.1q22), or t(16;16)(p13.1;q22) (mostly myelomonocytic leukaemia with preponderance of eosinophil granulocytes in the bone marrow) are the most favourable types of AML. Patients with normal karyotype AMLs are in an

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intermediate-risk group, and AMLs with complex karyotype abnormalities, and/or chromosomal monosomies fare particularly poorly.

In the MDSs, patients with partial deletion of genetic material from chromosome 5q (5q syndrome) or deletion of the Y chromosome are considered to be the most favourable category, and patients with MDS harbouring complex karyotype abnormalities, and/or chromosomal monosomies other than the 5q or –Y syndromes fare the worst. In MDSs a commonly used prognostic tool is the International Prognostic Scoring System (IPSS), recently modified to yield the World Prognostic Scoring System (WPSS), which in addition to blast percentage and cytogenetics also considers transfusion requirements in cytopenic patients. However, other systems have been or are being developed to improve prognostic scoring in MDSs.

molecular genetics

Good-risk translocations in AMLs defined above are all amenable to detection with molecular techniques (PCR or FISH) which may be faster than classical cytogenetics, and are therefore recommended. In cytogenetically normal AMLs, somatic mutations of the genes FLT3, NPM1 or CEBP α have been identified as important prognostic factors. NPM1 and CEBP α mutations are favourable when present as single mutations, whereas FLT3 alterations are not, irrespective of whether they occur on their own, in combination with NPM1 and CEBP α mutations, or with any karyotype alterations. Patients with abnormalities of the chromosomal region 11q23 representing the MLL (Mixed Lineage Leukaemia gene) fare poorly. Gene expression profiles assessed by microarray technology have been reported to split both AMLs and MDSs into defined sub-/categories, but these techniques are not yet ready for widespread routine use.

co-morbidity and other host factors

Patients aged ≥ 60 –65 years are more susceptible to treatment complications than younger patients, which contributes to their higher risk of an unfavourable outcome. Pre-existing medical conditions such as diabetes, coronary heart disease or chronic pulmonary obstructive disease must also be recognized as contributing to poor risk. To assess cardiac risk factors at diagnosis, in addition to clinical examination, cardiac echocardiography is recommended.

At diagnosis, patients should be investigated for the presence of active infection, particularly those planned for intensive treatment. In addition to clinical examination, additional techniques recommended are CT scans of the chest and abdomen, and radiological imaging of teeth and jaws to identify infectious foci such as dental root granulomas and caries. In addition to haematological and chemistry laboratory tests, a coagulation status must be obtained to detect leukaemia-related coagulopathy, particularly in APL; such tests must be performed before the insertion of central intravenous lines.

other pre-treatment investigations

Patients potentially suitable for allogeneic stem cell transplantation should be HLA typed at diagnosis, as should

their available first-degree family members. In high-risk disease (e.g. poor karyotype), early matched unrelated donor (MUD) allogeneic transplantation must be considered, and therefore, a donor search should be performed as early as possible.

treatment

Whenever possible, leukaemia treatment should be offered in clinical trials, and conducted only in experienced centres offering an adequate multidisciplinary infrastructure as well as a suitably high case load. In AMLs treatment should be planned with curative intent whenever possible, whilst in patients with MDS the goal of cure cannot often be reached. In contrast to AMLs, allogeneic stem cell transplantation (alloSCT) is the only curative treatment in MDSs, whereas a sizeable proportion of AML patients can be offered curative chances without alloSCT. Intensive treatment in AMLs and in selected patients with MDS suitable for this approach, is divided into an induction phase, consolidation and (rarely) maintenance chemotherapy. Potential AML or MDS candidates for alloSCT (scheduled for the consolidation phase) must be identified early at diagnosis or during induction chemotherapy.

intensive treatment of AMLs and MDSs

Induction chemotherapy should only be started (if possible) when all material needed for diagnostic tests has been satisfactorily sampled. Patients with excessive leukocytosis at presentation may require emergency leukapheresis before commencing chemotherapy.

Induction chemotherapy should include an anthracycline and cytosine arabinoside, with the '3+7' regimen particularly well known. APL induction chemotherapy consists of all-trans retinoic acid (ATRA) as a differentiating agent and an anthracycline, but the role of cytarabine in the treatment of APL is controversial. These patients must be followed very closely for the development of leukaemia-associated coagulopathy. Haematopoietic growth factors are an optional adjunct to intensive induction chemotherapy, and their role in priming leukaemic cells to become more sensitive to the cytostatic agents during induction remains to be confirmed.

Consolidation therapy in AML and MDS is warranted once patients have reached clinical and haematological remission. There is no consensus on a single 'best' post-remission treatment schedule. Patients who are unsuitable for alloSCT should receive intensive consolidation chemotherapy, preferably incorporating high-dose cytarabine into the consolidation regimen. In good-risk patients, who have a relapse risk of $\leq 35\%$, alloSCT is not justified in first remission because the risk of toxicity and/or transplantation-related mortality exceeds the benefit. Patients with AML in intermediate- and poor-risk groups, as well as higher-risk MDS patients with an HLA-identical sibling are candidates for alloSCT, provided their age and performance status allow for such treatment. Patients in these risk groups without a family donor may qualify for alloSCT with an HLA-matched unrelated donor identified through an international donor registry. If a killer-immunoglobulin-like receptor (KIR) mismatch is present, haploidentical transplants may be considered.

Conditioning regimens with dose-reduced intensity may be used for patients in the upper age range (particularly those >50 years of age). Infectious disease complications contracted during induction should be under suitable control before an alloSCT is enacted. The role of high-dose chemotherapy with autologous stem cell retransfusion in AMLs or MDSs is still controversial. Whilst it may prolong time to relapse or remission duration, its potential to prolong overall survival is uncertain. Maintenance therapy has been firmly established for first-remission APL only, where a combination of long-term chemotherapy and ATRA is warranted.

non-intensive treatment of MDS and AML

Patients with significant co-morbidity, the elderly, thus including many patients with MDS, are often not eligible for intensive treatment, and they should receive best supportive care (BSC) or palliative systemic treatment. Excessive leukocytosis due to spilling of malignant blasts into the periphery may be reduced with cytoreductive agents such as hydroxyurea or low-dose cytarabine, drugs that also reduce normal blood cells such as red cells, neutrophils or platelets. In BSC, treatment of infections due to neutropenia and transfusions to cover anaemia or thrombocytopenia are important measures for both AMLs and MDSs. Erythroid and myeloid growth factors are commonly used as part of supportive measures in MDSs, but their effect on the natural history is ill known.

In MDSs with low cell counts in the bone marrow (hypoplastic MDS) immunomodulatory treatment (similar to aplastic anaemia) may be offered, e.g. antithymocyte globulin, with limited success. MDS patients with the 5q syndrome may be treated with lenalidomide which obtains cytogenetic responses in half of them, and significantly reduces their red cell transfusion requirements. MDS patients may also be candidates for treatment with drugs inhibiting DNA methyltransferase (e.g. 5-azacytidine, or 5-aza-2'-deoxycytidine/decitabine). Randomized comparisons of 5-azacytidine against low-dose cytarabine or BSC have shown some survival benefit, particularly for patients with chromosome 7 alterations, whilst trials comparing decitabine with BSC have been negative in this respect.

therapy of refractory or relapsed AML or MDS

Patients failing to respond to one or two cycles of induction treatment are considered refractory, and are at very high risk of ultimate treatment failure. Carefully selected patients with an HLA-matched donor may be offered alloSCT, albeit with very limited chances of success, and at the cost of considerable morbidity from this procedure. For patients unsuited to this approach, BSC or palliative systemic treatment is often a reasonable option with at least limited toxicity. The prognosis of such patients is often dismal regardless of treatment attempts.

Patients presenting with relapse after a first remission may be offered intensive re-induction, where chances of success are better after longer duration of first remission. Patients in second or subsequent remission may still qualify for alloSCT with a family or unrelated HLA-matched donor. In relapsed

APL, arsenic trioxide can induce remissions, even in patients who have turned refractory to ATRA. The role of arsenic trioxide in first line therapy of APL, however, is not yet clearly settled.

response evaluation and follow-up

Response of AML or MDS to treatment is monitored clinically, with serial peripheral blood counts and repeat bone marrow examinations. During intensive chemotherapy, bone marrow should be examined in the aplastic phase to monitor blast clearance, persistence or early relapse. The usually accepted criteria of response in AMLs and MDSs are blast clearance in the bone marrow to <5% of all nucleated cells, morphologically normal haematopoiesis and return of peripheral blood cell counts to normal levels. Clearance of infections contracted during therapy-induced aplasia should also be documented.

Patients having concluded treatment should be followed clinically and with repeated haematological examinations. Serial bone marrow examinations of patients in remission are of uncertain value, and cannot therefore be generally recommended. Although sensitive PCR methods are available permitting molecular follow-up for patients with suitable markers (mostly specific chromosomal translocations), the early detection of molecular relapse in the absence of morphological evidence for recurrent leukaemia or MDS is of uncertain therapeutic consequence. Specifically evidence that early reinduction treatment of such patients still in haematological remission would be of any benefit is lacking.

note

Levels of Evidence (I–V) and Grades of Recommendation (A–D) are used as recommended by the American Society of Clinical Oncology. Statements in the text that were not graded, were considered otherwise justified clinical practice by the experts and reviewers, and the ESMO faculty.

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