LEUKEMIA

Response in Acute Myeloid Leukemia (AML)

Staging and response criteria in Acute Myeloid Leukemia for SWOG protocols activated prior to 2016 is based on the 2010 WHO Classification (see review article “Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel on behalf of the European Leukemia Net” (Döhner, et al., Blood, 2010. 115(3):453-474). Staging and response criteria in Acute Myeloid Leukemia for SWOG protocols activated after 2016 is based on 2016 updated WHO Classification of Myeloid Neoplasms and Acute Leukemia (see review article “Diagnosis and Management of AML in Adults: 2017 ELN Recommendations from an International Expert Panel.” (Dohner et al., Blood, pre-published online 2016. doi: 10.1182/blood-2016-08-733196). The WHO definitions of AML have been adopted over the previously used FAB definitions.

As with all SWOG protocols please refer to Section 4 for staging criteria when determining eligibility and to Section 10 for response criteria. This chapter lists general guidelines, but treatment protocols may vary in their definitions of response. Be sure that you are following the staging and response criteria listed in the current version of your patient's protocol.

Diagnostic and Staging Criteria (per 2016 updated WHO Classification)

Definitions:

1. Bone marrow cellularity: The volume of hematopoietic nucleated cells, expressed as a percentage of marrow volume less volume of fibrosis.
2. Blasts: For AML, the following cell types are considered equivalent to blasts and are included in the calculation of blast percentages. Note that erythroblasts are not counted as blasts in calculating blast percentages.
   i. Myeloblasts include both agranular and granular variants.
   ii. Neoplastic promyelocytes, for Acute Promyelocytic Leukemia. Neoplastic promyelocytes are defined as promyelocytes with heavy granulation and irregular nuclei and/or primitive promyelocytes with very large numerous Auer rods.
   iii. Monoblasts and promonocytes for Acute Monoblastic and Monocytic Leukemia.
   iv. Megakaryoblasts for Acute Megakaryoblastic Leukemia.
3. Bone Marrow Blast Percentage is calculated as the percent of blasts among all nucleated marrow cells.

Acute Myeloid Leukemia (AML) is a clonal expansion of myeloid blasts in bone marrow, blood or other tissue, ICD-O code 9861/3. With the 2016 WHO classification, AML is defined by ≥ 20% myeloblasts in the blood or marrow. The exception for acute erythroid leukemia has been removed from the definition of AML.
Remission Definitions for AML (per the 2017 ELN AML Recommendations):

1. Complete remission (CR): Bone marrow blasts <5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count >1.0 x 10^9/L (1,000/µL) and platelet count >100 x 10^9/L (100,000/µL).
2. Complete remission with incomplete hematologic recovery (CRi): All CR criteria except for residual neutropenia [<1.0 x 10^9/L (1,000/µL)] or thrombocytopenia [<100 x 10^9/L (100,000/µL)].
3. Partial remission (PR): All hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%.

Response in Other Acute Leukemia and Blast Phase Chronic Myelogenous Leukemia

Listed below are the basic criteria used in studies of acute leukemia (i.e., acute promyelocytic leukemia or APL and acute lymphocytic leukemia or ALL) and chronic myelogenous leukemia (CML) in blast phase. Always refer to the specific protocol for response criteria for that study.

Disease Status Criteria for APL:

Note that the kinds of cells considered equivalent to blasts and included in the calculation of blast percentage are defined in section 4 of the treatment protocol.

Blasts cells, for Acute Promyelocytic Leukemia: Neoplastic promyelocytes are defined as promyelocytes with heavy granulation and irregular nuclei and/or primitive promyelocytes with very large numerous Auer rods.

a. Bone Marrow:
   A1. Maturation of all cell lines: and <5% blasts and no Auer rods.
   A2. Same as A1, except blasts ≥5% and <25%.
   A3. Failure to meet the criteria for A1 or A2.

b. Peripheral Blood:
   B1. Neutrophils > 1,000/mcl and platelets > 100,000/mcl and no leukemia blasts in the peripheral blood.
   B2. Failure to meet the criteria for B1.

c. Extramedullary Disease:
   C1. None
   C2. Any

Response Definitions:

**CR** Attainment of A1 marrow status and B1 peripheral blood status and C1 extramedullary disease status for a period of at least 28 days.
CR **with incomplete blood count recovery**: Same as CR but platelets ≤ 100,000/mcl and/or neutrophils ≤ 1,000/mcl.

PR **Partial Response**: All of the above criteria for CR must be met, except that the bone marrow may contain ≥ 5% but less than 25% blasts, or ≤ 5% blasts in the presence of Auer rods or abnormal morphology.

**FAILURE --resistant disease**

Resistant Disease: Patient survives ≥ 7 days following completion of initial treatment course with persistent leukemia in the last peripheral blood smear or bone marrow, or with persistent extramedullary disease.

**FAILURE - aplasia**

Aplasia: Patient survives ≥ 7 days following completion of initial treatment course then dies while cytopenic, with the last post-induction bone marrow aplastic or hypoplastic (i.e. < 20% cellularity) and without leukemia blasts.

**FAILURE - indeterminate**

Indeterminate: (a) Patient survives < 7 days after completion of initial treatment course; or (b) patient survives ≥ 7 days following completion of initial treatment course then dies with no persistent leukemia in the peripheral smear but no post-induction bone marrow examination.

**RELAPSE FROM CR**

Relapse: Reappearance of leukemia blasts in the peripheral blood; or > 5% blasts in the bone marrow not attributable to another cause (e.g., recovery of normal cells following chemotherapy-induced aplasia); or appearance or reappearance of extramedullary disease.

**Disease Status Criteria for ALL**

At least 20% lymphoblasts present in blood or marrow at baseline. Immunophenotyping must be performed to determine lineage (B cell, T cell or mixed B/T cell)

Extramedullary Disease in ALL:

a. Measurable Extramedullary Disease: Lesions that can be accurately measured in two dimensions by CT, MRI, medical photograph (skin or oral lesion), plain x-ray, or other conventional technique and a greatest transverse diameter of 1 cm or greater; or palpable lesions with both diameters ≥ 2 cm. Note: CT scans remain the standard for evaluation of nodal disease.

b. Non-measurable Extramedullary Disease: All other lesions including unidimensional lesions, lesions too small to be considered measurable, pleural or pericardial effusion, ascites, bone disease, leptomeningeal disease, lymphangitis, pulmonitis, abdominal masses not confirmed or followed by imaging techniques or disease documented by indirect evidence only (e.g., lab values).
**C1**: Complete disappearance of all measurable and non-measurable extramedullary disease with the exception of lesions for which the following must be true: for patients with at least one measurable lesion, all nodal masses > 1.5 cm in greatest transverse diameter (GTD) at baseline must have regressed to ≤ 1.5 cm in GTD and all nodal masses ≥ 1 cm and ≤ 1.5 cm in GTD at baseline must have regressed to < 1 cm GTD or they must have reduced by 75% in sum of products of greatest diameters (SPD). No new lesions. Spleen and other previously enlarged organs must have regressed in size and must not be palpable. All disease must be assessed using the same technique as at baseline.

**C2**: Patient does not qualify for C1 status.

**Complete Remission (CR)**
   a. < 5% marrow aspirate blasts. Blasts can be ≥ 5% if the blasts are found to be myeloid and there is no evidence of lymphoblasts by flow cytometry or immunostaining.
   b. Neutrophils (ANC) ≥ 1,000/mcI; platelets > 100,000/mcI; and no blasts in the peripheral blood.
   c. C1 Extramedullary disease status (see above)

**Complete Remission with Incomplete Platelet Recovery (CRi)**
Same as CR but platelet count may be ≤ 100,000/mcI and/or ANC ≤ 1,000/mcI

**Partial remission (PR)**
Improvement or no worsening of ALL, as indicated by all of the following:
   a. No blasts in the peripheral blood
   b. Neutrophils (ANC) ≥ 1,000/mcI; platelets > 100,000/mcI
   c. Either or both of the following:
      1. At least a 50% decrease in the marrow blast percentage, compared to the pretreatment value, and marrow blast percentage ≥ 5% and ≤ 25%.
      2. C2 extramedullary disease status as described above.

Definitions for Failure to respond and Relapse from CR are the same as noted above for APL.

**Response in Other Leukemias and Myelodysplastic Syndrome**
The response criteria for other leukemia (CML in chronic or accelerated phase, chronic lymphocytic leukemia or CLL, hairy cell leukemia, and other leukemias) and for myelodysplastic syndrome (MDS) are given in each study protocol in Section 10.


Response criteria for CML are based on RT-PCR to measure BCR-ABL transcripts (molecular response).

Baseline and Follow-up Studies

Typical studies include: complete blood count (CBC) with differential and platelet count, bone marrow biopsy and aspirate, and clinical evaluation of extramedullary disease. For CML, molecular response is assessed by RT-PCR to measure BCR-ABL transcript levels. This is done in commercial labs as standard-of-care monitoring.

AML RESPONSE EXERCISES

The following exercises distinguish between ‘response/endpoint’ and ‘best response’. Response/endpoint refers to the patient’s response at each scheduled assessment. Best response is the patient’s most favorable response over all assessments.

Exercise 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Prestudy</th>
<th>Day 21</th>
<th>Day 60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marrow blast %</td>
<td>90%</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>Auer Rods</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Neutrophils (ANC)</td>
<td>3,000</td>
<td>1,500</td>
<td>4,600</td>
</tr>
<tr>
<td>Platelets</td>
<td>95,000</td>
<td>51,000</td>
<td>150,000</td>
</tr>
<tr>
<td>Peripheral blast %</td>
<td>23%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Extramedullary ds</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Response/Endpoint</td>
<td>CRi</td>
<td>CR</td>
<td></td>
</tr>
<tr>
<td>Best Response</td>
<td></td>
<td>CR</td>
<td></td>
</tr>
</tbody>
</table>

Note that day 21 meets criteria for remission except that platelets are not yet > 100,000 (CRi). Day 60 results show a CR.

Exercise 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Prestudy</th>
<th>Day 14</th>
<th>Day 40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marrow blast %</td>
<td>98%</td>
<td>8%</td>
<td>0%</td>
</tr>
<tr>
<td>Auer Rods</td>
<td>present</td>
<td>present</td>
<td>none</td>
</tr>
<tr>
<td>Neutrophils (ANC)</td>
<td>1,700</td>
<td>300</td>
<td>1,800</td>
</tr>
<tr>
<td>Platelets</td>
<td>22,000</td>
<td>8,000</td>
<td>130,000</td>
</tr>
<tr>
<td>Peripheral blast %</td>
<td>76%</td>
<td>23%</td>
<td>0%</td>
</tr>
<tr>
<td>Extramedullary ds</td>
<td>csf +</td>
<td>csf +</td>
<td>csf -</td>
</tr>
<tr>
<td>Response/Endpoint</td>
<td>Pending</td>
<td>CR</td>
<td></td>
</tr>
<tr>
<td>Best Response</td>
<td></td>
<td>CR</td>
<td></td>
</tr>
</tbody>
</table>

This patient required a second induction course of treatment following the day 14 assessment. The patient first met the criteria for complete remission on Day 40.
Exercise 3

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Prestudy</th>
<th>Day 21</th>
<th>Day 75</th>
<th>Day 78</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marrow blast %</td>
<td>90%</td>
<td>0%</td>
<td>not done</td>
<td>22%</td>
</tr>
<tr>
<td>Auer Rods</td>
<td>present</td>
<td>none</td>
<td>not done</td>
<td>present</td>
</tr>
<tr>
<td>Neutrophils (ANC)</td>
<td>3,000</td>
<td>1,550</td>
<td>6,000</td>
<td>4,600</td>
</tr>
<tr>
<td>Platelets</td>
<td>82,000</td>
<td>103,000</td>
<td>150,000</td>
<td>124,000</td>
</tr>
<tr>
<td>Peripheral blast %</td>
<td>35%</td>
<td>0%</td>
<td>12%</td>
<td>9%</td>
</tr>
<tr>
<td>Extramedullary ds</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Response/Endpoint</td>
<td>none</td>
<td>CR</td>
<td>Relapse</td>
<td>Relapse</td>
</tr>
<tr>
<td>Best Response</td>
<td></td>
<td></td>
<td></td>
<td>CR</td>
</tr>
</tbody>
</table>

This patient achieved complete remission on day 21. Relapse was detected on day 75 by the appearance of blasts in the peripheral blood, confirmed 3 days later by bone marrow examination; therefore, day 75 is day of relapse. Best response is the CR on day 21.