Secondary leukemia - Section 2

Epidemiology and impact of preceding or underlying disease in secondary acute myeloid leukemia

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Definition and epidemiology of sAML

Secondary AML (sAML) is defined as AML occurring after an antecedent myeloid disease (i.e. myelodysplastic syndrome [MDS] or myeloproliferative neoplasia [MPN], regardless of prior cytotoxic therapy). Therapy-related AML, which is often categorized with sAML, will not be further discussed in this section. Though incorporating biological prognostic features refined earlier strict clinical definition, MDS or MPN history alone remains a diagnostic criterion.1 Recent studies reported that sAML accounts for ~20% of AML. The median age at presentation is higher than in de novo and therapy-related AML.2 However, also among patients receiving induction chemotherapy, sAML patients are half as likely to be enrolled in clinical trials compared to de novo AML patients3 potentially reflecting physician and/or patient treatment selection bias towards non-intensive treatment options in these patients.

Leukemic transformation in underlying disease

MDS

Most sAML cases arise from MDS (~60%).4,5 Patients with low-risk MDS have a 10-15% risk of transformation compared to 40-50% in higher-risk MDS, with the risk being constant over time, at least in low-risk MDS, suggesting that a single critical biological hit determines AML transformation.4 Clonal architecture studies have found MDS and sAML to be oligoclonal diseases with sAML deriving from a founding or one of many early-mutated MDS clones.5 Normal karyotype is common in MDS patients. Still, more than 80% harbor one or more genomic abnormality at diagnosis.7 The broad spectrum of mutations contributes to the clinical heterogeneity of MDS. Even among patients with early MDS, more than 90% of patients harbor mutations in a morphological nondiagnostic bone marrow sample with IDH2 and TP53 mutations predicting shorter time to AML progression and poorer overall survival.8 At time of transplantation, presence of somatic mutations also affects outcomes in MDS and sAML patients with RUNX1, ASXL1, or TP53 mutations independently predicting higher risk of relapse.9 Though several mutations have shown to independently predict disease progression and overall survival, the Revised International Prognostic Scoring System (IPSS-R) remains the gold standard in MDS.10 Recent studies, however, have demonstrated that addition of mutational data to the IPSS-R enhances its predictive ability in treated MDS patients.11

CMML

CMML shares overlapping features of MDS and MPN and precedes sAML in 11% of the cases.5,12 AML transformation following CMML occurs in ~15-50% depending on prognostic features. Normal karyotype is observed in 60-80% of patients with CMML, but less frequent cytogenetic alterations, including monosomy 7, trisomy 8, and complex karyotype, are associated with increased risk of AML transformation.13 In addition, ~90% of patients present with cytogenetically-silent gene mutations, including SRSF2, TET2, and/or ASXL1.14 Previous studies show that cytogenetic and molecular abnormalities provide better risk assessment and prognostication, with ASXL1 mutations predicting aggressive disease behavior with shorter time to AML and inferior overall survival. Using molecular and cytogenetics
alongside clinical parameters identifies CMML patients with no/very low risk of AML progression in 1/3 of cases.\textsuperscript{12,14}

**MPN**

Polycythemia vera (PV) precedes 11-13\% of sAML cases, essential thrombocythemia (ET) 4-7\%, and myelofibrosis 11\%.\textsuperscript{2,4} The overall risk of AML progression in primary or secondary (post-PV or post-ET) myelofibrosis exceeds 10\%. The revised WHO 2016 criteria (overt-PMF vs pre-MF) and grade of fibrosis independently predict a higher risk of transformation.\textsuperscript{1,13} Recently, ASXL1, EZH2, and SRSF2 mutations identified high-risk patients, however, only CALR and ASXL1 showed negative prognostic value independently of available prognostication tools based on clinical and cytogenetic information.\textsuperscript{16} In PV and ET, the 10-year transformation risk is <10\%.\textsuperscript{17} Mutational status and cytogenetic changes in MPN correlate well with disease stage, as the proportion of abnormal karyotype increases rapidly from diagnosis to blast phase (20-90\%) with a dynamic pattern of more complex karyotypes in the more advanced stages.\textsuperscript{18}

**Prognostic impact of clinical features and underlying disease**

Outcome in sAML depends on multiple patient- and disease-related factors. Information on unselected sAML patients is limited, and direct comparison of characteristics and outcomes to other clinically defined subgroups; therapy-related and de novo AML, is rare (Table 1). Prognostic differences between sAML and de novo patients include higher frequency of adverse-risk cytogenetic abnormalities in sAML and inferior survival.\textsuperscript{2,4} In addition, disease characteristics and outcome within sAML vary with preceding hematological disease. For example, a higher proportion of aberrant karyotype was found in non-MDS-sAML compared to MDS-sAML, which may reflect presence of RUNX1, TP53, or ASXL1 mutations. The study showed that patients with MDS-sAML who received remission-induction chemotherapy had inferior response rates and shorter overall survival compared with de novo AML.\textsuperscript{2} In non-MDS-sAML patients achieving a complete remission, remission duration was short-lived and induction-chemotherapy should be limited for patients potentially eligible for HSCT.\textsuperscript{2} Compared to de novo AML, fewer sAML will proceed to HSCT, however no differences in post-allotransplant outcomes were observed in patients with de novo or sAML undergoing HSCT in CR1.\textsuperscript{2,19} The difference in characteristics and outcomes reported in MDS-sAML and non-MDS-sAML suggest that leukemic transformation mechanisms in CMML and MPN may be biological different from those involved in MDS progression.\textsuperscript{2} Recently, it was shown that some AML patients showing myelodysplasia-related features and blast counts <30\% may have outcomes resembling that of MDS/de novo AML more than sAML,\textsuperscript{2,10} suggesting overlapping biological behavior.\textsuperscript{6} Differences between non-MDS and MDS-sAML may be caused by factors related to bone-marrow stromal environmental factors, non-reversible bone marrow fibrosis,\textsuperscript{20} or different molecular patterns resulting in treatment refractory and aggressive disease.

**Importance of molecular findings**

Unlike our knowledge about somatic mutation in sAML, little is known about importance of clonal architecture and individual molecular mutations in MDS, MPN and CMML at leukemic transformation. Inclusion of sAML patients in clonal architecture studies is needed to better understand leukemic transformation processes in these patients. Also, refinement of current clinical classification systems of sAML by integration of molecular genetic principles

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**Table 1. Characteristics of unselected de novo and sAML patients from two National Scandinavian cohorts.\textsuperscript{2,4}**

|                      | Swedish cohort (n=3104) |                | Danish cohort (n=3055) |
|----------------------|-------------------------|----------------|------------------------|
|                      | De novo AML (n=2474)    | sAML (n=630)  | De novo AML (n=2249)   | MDS-sAML (n=350) | Non-MDS-sAML (n=253) |
| Intensive therapy, % | 64%                     | 39%           | 55%                    | 38%            | 34%                 |
| Sex, male, %         | 50%                     | 58%           | 55%                    | 63%            | 56%                 |
| Median age, years (IQR) | 71 (56-80)            | 73 (56-80)    | 69 (56-78)             | 70 (63-78)     | 71 (64-77)          |
| Comorbidities, %     |                         |               |                        |                |                    |
| No comorbidities     | 66%                     | 52%           | 48%                    |                |                    |
| 1 comorbidity        | 23%                     | 29%           | 32%                    |                |                    |
| ≥2 comorbidities     | 12%                     | 19%           | 20%                    |                |                    |
| WHO performance status, % |                    |               |                        |                |                    |
| 0                    | 18%                     | 10%           | 27%                    | 21%            | 19%                 |
| 1                    | 39%                     | 38%           | 42%                    | 47%            | 39%                 |
| ≥2                   | 43%                     | 53%           | 31%                    | 33%            | 42%                 |
| Median blast count marrow, % (IQR) | 52 (30-78) | 35 (24-50) | 40 (24-58) |                |                    |
| Median WBC, x10\(^9\) (IQR) | 10 (2-51)           | 8 (2-36)      | 25 (8-50)              |                |                    |
| Platelet count, 10\(^9\) (IQR) | 55 (30-105) | 40 (20-86) | 48 (21-118) |                |                    |
| Cytogenetic risk group (MRO), % |                    |               |                        |                |                    |
| Favorable risk       | 9%                      | 1%            | 5%                     | 0%             | 1%                  |
| Intermediate risk    | 65%                     | 59%           | 74%                    | 70%            | 71%                 |
| Adverse risk         | 26%                     | 40%           | 21%                    | 30%            | 28%                 |
| Cytogenetics (karyotype), % |                    |               |                        |                |                    |
| Normal karyotype     | 51%                     | 47%           | 35%                    |                |                    |

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sAML, secondary acute myeloid leukemia; MDS, myelodysplastic syndrome; IQR, interquartile range; MRO, Medical Research Council.
into a biologically more precise disease classification may lead to greater diagnostic certainty and improved prognostication.

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