

Secondary acute myeloid leukemia: time to turn the page

Christian Récher

Service d'Hématologie, Centre Hospitalier Universitaire de Toulouse, Institut Universitaire du Cancer de Toulouse Oncopole, Université Toulouse III Paul Sabatier, Toulouse, France

Correspondence: C. RECHER

Recher.Christian@iuct-oncopole.fr


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In this issue of *Haematologica*, Martinez-Cuadron *et al.* have analyzed data from a multinational registry co-ordinated by the Spanish Programa de Estudio y Tratamiento de las Hemopatías Malignas (PETHEMA) and report the results of intensive treatments that were available before the era of new therapeutic options in older patients with secondary acute myeloid leukemia (AML).¹ For physicians used to treating AML, the terms “elderly” or “secondary” have always been synonymous with major problems of patient and disease management. The combination of these two factors results in one of the worst prognoses in oncology, underlying the urgent need for innovative research. For the academics who classify hematologic malignancies, the definition of secondary AML has remained an evolving field in view of recent advances in the molecular characterization of AML with the aim to rationally define patient populations. In everyday language, “secondary” AML encompass therapy-related AML (t-AML) that occur after prior exposure to cytotoxic chemotherapy and/or radiotherapy, and AML that occur after a previous myeloid malignancy such as myelodysplastic syndrome (MDS) or MDS/myeloproliferative neoplasms (MPN).

PETHEMA is to be congratulated on having set up such a large registry, thus making it possible to produce one of the largest cohorts of patients with secondary AML who were selected by their physicians in routine practice to receive intensive chemotherapy. The richness of the data is particularly appreciated. The investigators focused on a patient population with criteria similar to that of the pivotal phase III trial comparing standard chemotherapy and the liposomal encapsulation of cytarabine and daunorubicin CPX-351, which led to the registration of CPX-351 for t-AML and AML with myelodysplasia-related changes (AML-MRC).² As expected, the results confirm the poor prognosis of intensive chemotherapy in a real-world setting. Again, not surprisingly, age and poor performance status were adverse prognostic factors for response and overall survival, while favorable/intermediate cytogenetic risk and *NPM1* mutations were favorable factors. Post-remission therapy also affected outcome, especially hematopoietic stem cell transplantation (HCT).

This study raises several points for discussion. Firstly, this picture of real-life practice shows that patients were selected for intensive therapy mainly according to criteria such as age and performance status, rather than on chemosensitivity. Secondly, only a minority of patients who were refractory to a first induction cycle received a second cycle. It is likely that physicians estimated that in the light of the benefit/risk ratio, a second induction was of little value, which, in this specific situation, is probably true. In the European LeukemiaNet 2022 guidelines, however, patients are considered to be refractory if they complete two cycles of induction.³ Since eligibility criteria for clinical trials generally follow this recommendation, this may be of concern for those patients who, having failed a first cycle, could then proceed directly to innovative therapy rather than undergo another futile, and potentially toxic, cycle of chemotherapy.⁴ Third, although in this patient population bridging to allogeneic HSCT (alloHCT) after induction chemotherapy is a major therapeutic goal, only a minority of patients received transplants, thus leaving room for maintenance therapy for those patients who were able to achieve complete remission. Lastly, even though in secondary AML, *NPM1* mutations are a rare event, they retain a major prognostic impact; in fact, recent data showed that therapy-related and *de novo* mutated *NPM1* AML have overlapping features and a similar prognosis.⁵ Therefore, t-AML and sAML with *NPM1* mutation should be managed as *de novo* AML.

This study is likely to be one of the last to evaluate standard chemotherapy in this predefined population, as the definition of secondary AML has now been refined and treatment has been changed. Although in certain respects the recent World Health Organization classification differs from the latest International Consensus Classification, both have significantly modified the subentities of secondary AML: AML-MRC and t-AML have been removed,^{6,7} and the International Consensus Classification has isolated AML with *TP53* mutations as a single entity. Previous exposure to cytotoxic therapy (which now includes immune interventions and PARP inhibitors) and prior MDS or MDS/MPN are now diagnostic

qualifiers of disease entities. AML-MRC have been replaced by a new entity, myelodysplasia-related AML (AML-MR), which is biologically defined by specific cytogenetic or molecular abnormalities (secondary AML-like mutations) but no longer by multilineage dysplasia. Meanwhile, novel therapeutic strategies have been developed, including CPX-351, which have proven efficacy over standard 3+7 with lower extra-hematologic toxicity and an impressive outcome in patients who were bridged to alloHCT. However, CPX-351 was specifically approved in the formerly defined-group of t-AML and AML-MRC. By introducing secondary AML-like mutations in the new AML-MR definitions, a sizable proportion of *de novo*

intermediate-risk AML who were not included in the pivotal trial have now been reclassified. Whether CPX-351 is also of benefit in AML with MR-gene mutations receptor gene mutations compared to standard chemotherapy is an open question. Venetoclax plus azacitidine (VEN-AZA) has also demonstrated significant activity in secondary AML.⁸ Although this combination has been approved for patients who are ineligible for intensive chemotherapy, many physicians propose VEN-AZA in high-risk AML as a bridge to transplantation in fit patients. Lastly, targeted agents, such as IDH or FLT3 inhibitors, added to standard chemotherapy may also improve outcome in high-risk patients, and maintenance

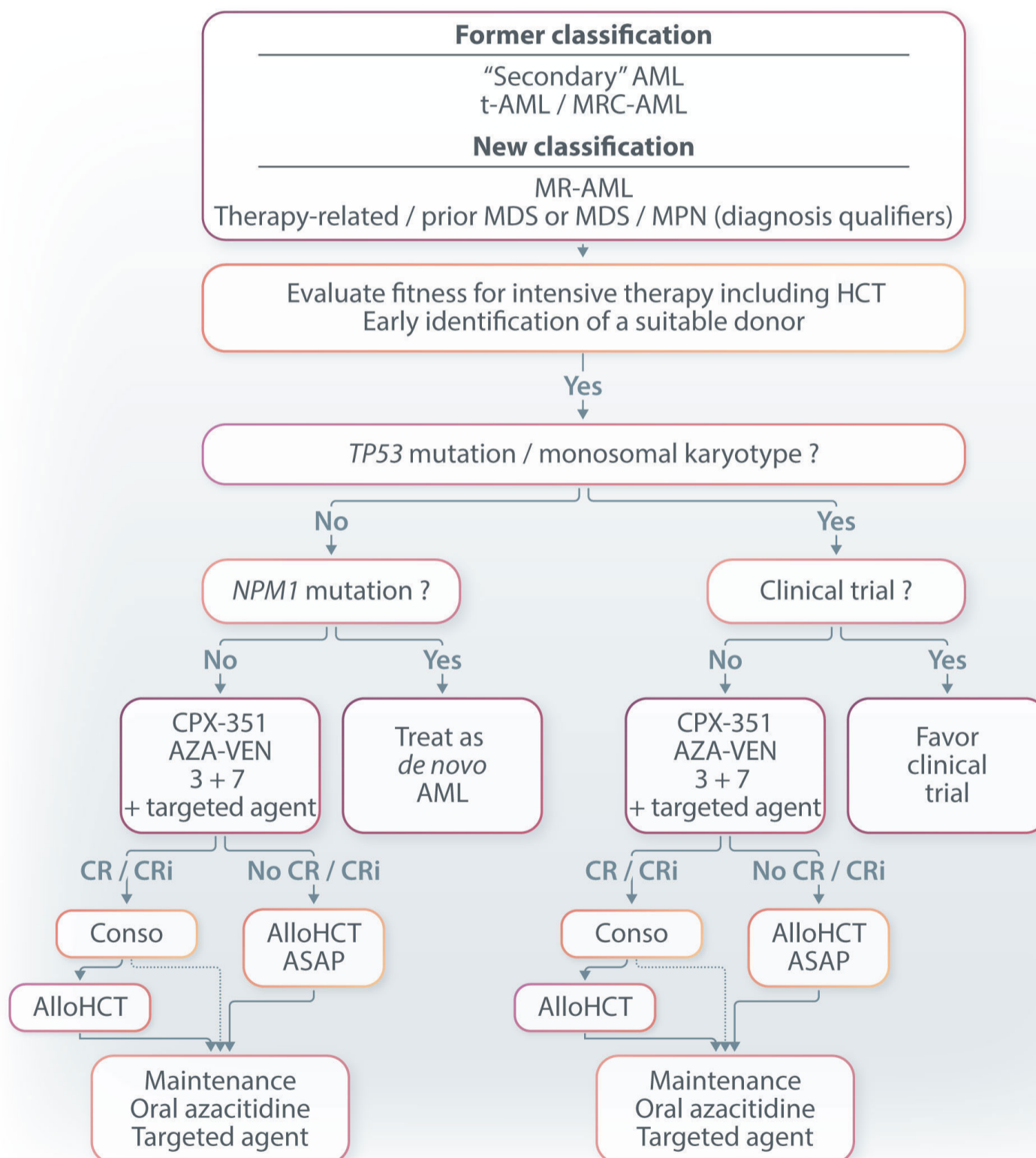


Figure 1. Management algorithm for secondary acute myeloid leukemia. alloHCT: allogeneic hematopoietic stem cell transplantation; ASAP: as soon as possible; Conso: consolidation chemotherapy; AML: acute myeloid leukemia; t-AML: therapy-related AML; MR-AML: myelodysplasia-related AML; MRC-AML: AML with myelodysplasia-related changes; MDS: myelodysplastic syndrome; MPN: myeloproliferative neoplasms; AZA-VEN: azacitidine venetoclax; CR/CRi: complete remission/CR with incomplete hematologic recovery.

therapy with oral AZA prolongs the duration of both response and survival.⁹

Things are also moving in the field of transplantation, which is crucial for long-term survival. A recent randomized trial convincingly demonstrated that sequential conditioning and immediate transplantation produce similar outcomes to intensive remission induction chemotherapy followed by alloHCT in refractory or relapsed AML.¹⁰ This strategy should undoubtedly facilitate bridging to transplantation in a significant proportion of patients. Therefore, as soon as the diagnosis is made, the treatment strategy for patients with secondary AML should integrate an active search for a suitable donor with a transplant schedule. While awaiting transplantation, achieving disease control and eventually reaching complete remission

without compromising general health is highly desirable, and CPX351 or VEN-AZA appear to fulfill this mission better than 3+7 (Figure 1). Preventing post-transplant relapse is also becoming an important issue.

To sum up, the therapeutic landscape for front-line treatment in secondary AML has changed dramatically and brings hope for better outcomes. A registry such as this will surely provide the PETHEMA group with the opportunity to show us the impact of these new treatments in real-life clinical practice.

Disclosures

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