Improving consolidation therapy in acute myeloid leukemia - a tough nut to crack

Richard F. Schlenk,[1,2] Sonia Jaramillo[2] and Carsten Müller-Tidow[2]

[1]NCT-Trial Center, National Center for Tumor Diseases, German Cancer Research Center, Heidelberg, and [2]Department of Hematology, Oncology, and Rheumatology at Heidelberg University Hospital, University of Heidelberg, Germany

E-mail: richard.schlenk@nct-heidelberg.de

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After intensive induction therapy, 60% to 80% of younger (≤60 years) and 40% to 60% of older (>60 years) patients with acute myeloid leukemia (AML) achieve a complete remission.[1] However, despite intensive consolidation therapy including intensive chemotherapy, autologous or allogeneic hematopoietic cell transplantation approximately half of younger and 80% to 90% of older patients relapse and the majority of relapsed patients succumb to their disease.[2] Based on these figures, it is expected that prevention of relapse by better consolidation therapy would immediately translate into better overall survival. This interrelationship appears to be simple but it is now 24 years ago that this could be demonstrated in a randomized clinical trial that showed a dose-response effect for cytarabine, with improved relapse-free and overall survival among the patients receiving high-dose cytarabine,[3] which remains a cornerstone of consolidation chemotherapy in AML.[1,4,5]

In this issue of *Haematologica*, Burnett and colleagues report on a randomized comparison evaluating the addition of the mammalian target of rapamycin inhibitor, everolimus, to consolidation therapy in AML.[6] Everolimus was given for a maximum of 84 days between chemotherapy courses in the experimental arm of the study. Despite the pre-clinical *in vitro* and *in vivo* rationale for everolimus, further supported by promising clinical data from phase I/II trials, the independent Data Monitoring Committee (DMC) advised study termination after randomization of 339 patients (2:1 ratio) due to excessive mortality in the everolimus arm. Toxicity of everolimus was primarily gastrointestinal (mucositis and diarrhea) and biochemical evidence of liver toxicity. The primary reason for increased mortality was infection-related deaths within the first 6 months of treatment mainly due to the immunosuppressive effects of everolimus, which reflects what has been seen with the use of this drug in solid tumors.[7]

This is a remarkable study and we would like to highlight two aspects: (i) the important role of the DMC in taking care of patients' safety, (ii) the issue of whether we have the right strategies to improve results in consolidation therapy.

Overall, the DMC played a very active role in the study by first recommending dose-reduction for the starting dose from 10 mg to 5 mg after randomization of 146 patients, based on the observation of increased side effects and reduced compliance; the DMC then recommended stopping the trial prematurely after randomization of 339 of the intended 600 patients. These DMC decisions were based, at those time points during the study, on incomplete datasets and were associated with some uncertainty and thus the decisions were not easy to take.[8] In hindsight, with more trial data available, these decisions were clearly justified and prevented exposure of additional patients to an increased risk of death. This trial is, therefore, a good example of successful DMC work with useful recommendations at the right time points during a study. This underlines the importance of anticipating risks already in the planning phase of a clinical trial, incorporating the identified risks into the statistical design and structure of a study with predefined interim analyses, selecting appropriate DMC members with engagement at the interim analyses as well as unscheduled analyses if necessary and, finally, of having an experienced and alert study team.

The second interesting aspect of the study which we like to focus on is whether we are using the right strategy to improve consolidation therapy in AML. Based on favorable results with mammalian target of rapamycin inhibitors in preclinical models and clinical phase I/II studies in patients with active disease (newly diagnosed or relapsed AML), everolimus was added in the UK NCRI AML17 trial to consolidation therapy for patients who were in first complete remission. One assumption behind this approach is that effective biological mechanisms of action are similar during induction treatment and during consolidation therapy with residual leukemic cells hidden in bone marrow niches. It became apparent that this was not the case: in contrast to the encouraging results of everolimus in patients with active disease, the use of this inhibitor as an add-on to standard consolidation chemotherapy was associated with increased toxicity and a significant excess of deaths in remission. Even more disappointing was the fact that there was no evidence that everolimus is effective in preventing relapses. Interestingly, this mirrors data from clinical trials evaluating midostaurin and gemtuzumab ozogamicin (GO).

Based on the pivotal large international multicenter randomized double-blinded phase III trial (CALGB 10603, RATIFY, clinicaltrials.gov: NCT00651261) in young adults (18-59 years) with *FLT3*-mutated AML, the US Food & Drug Administration (FDA) and the European Medicines Agency (EMA) recently approved midostaurin as an adjunct to conventional chemotherapy, including induction and post-remission therapy, without an upper age limit.[9] A debate is ongoing how midostaurin affects overall survival and about the role of midostaurin in consolidation and maintenance therapy. A recent exploratory analysis of the trial revealed that midostaurin most effectively prevented relapse in patients who underwent allogeneic hematopoietic cell transplantation in first complete remission. These patients had a trend to better survival (P=0.07) and a significantly lower cumulative incidence of relapse (P=0.02).[10] In contrast, patients in first complete remission who received high-dose cytarabine consolidation therapy had a comparable cumulative incidence of relapse rate whether they received midostaurin or not. Thus again, there is no clear evidence that midostaurin given as add-on therapy to high-dose cytarabine prevents relapse. In fact, the addition of midostaurin to first induction therapy seems to have the greatest impact on the observed beneficial effect on event-free and overall survival.[9]

Based on the results of the ALFA-0701 (NCT00927498)

study in newly diagnosed patients,[11] the AML-19 study in patients with newly diagnosed AML unsuitable for intensive chemotherapy,[12] and the MyloFrance-1 study in relapsed/refractory AML,[13] GO was reapproved by the FDA in 2017 for the treatment of newly-diagnosed CD33+ AML in adults and treatment of relapsed or refractory CD33+ AML in adults and in pediatric patients 2 years and older. In Europe, GO was approved in 2018 for the treatment of patients aged 15 years and older with previously untreated, *de novo*, CD33+ AML. Both approvals (FDA, EMA) for newly-diagnosed CD33+ AML in adults included the addition of GO (3 mg/m^2, day 1) to consolidation therapy with daunorubicin and cytarabine. However, in two trials assessing GO administered on a randomized basis in post-remission therapy, no significant impact on survival was observed.[14,15] In the MRC AML-15 trial a total of 948 patients were randomly assigned to receive or not receive GO as an adjunct to first consolidation therapy.[14] Once again, there was no evidence that relapses were prevented (P=0.20) and the overall survival rates of the patients in the two groups were nearly superimposable (hazard ratio, 1.02; 95% confidence interval: 0.82-1.27). In a study of the HOVON group, older patients achieving complete remission after intensive induction therapy were randomized to three cycles of GO (6 mg/m^2 every 4 weeks) or no postremission therapy.[15] The two treatment groups (113 patients receiving GO *versus* 119 control patients) were comparable with respect to age, performance status, and cytogenetics. There were no significant differences between the groups with regard to overall survival (P=0.52) and disease-free survival (P=0.40).

These examples consistently show that new drugs that are active as an adjunctive therapy to standard induction are not necessarily active in consolidation therapy. But why is this the case and how can we improve the situation? In AML patients with active disease (newly diagnosed, relapsed or refractory) there is usually a bulk population of leukemic cells which can be characterized in depth by sophisticated methods and treated with targeted drugs if the target is present, such as activating *FLT3* mutations, CD33 expression, or probably active AKT signaling. In contrast, the clinical situation of consolidation therapy is currently difficult to model *in vitro* or *in vivo*. Therefore, the preclinical evidence available before the initiation of a clinical trial is often limited. For example, the senescence-associated reprogramming of non-stem bulk leukemia cells into self-renewing, leukemia-initiating stem cells,[16] which may occur during the course of AML treatment, is currently not assessed within clinical trials. It is, therefore, of the utmost importance that methodologies of stem cell research are adapted to be fit for the purpose of use in clinical studies, particularly addressing consolidation research questions.

We also need to improve the sensitivity and specificity of our methods of describing the depth of remission during the consolidation treatment phase. The term molecular remission has been introduced in current guidelines.[1,5] Nevertheless, consolidation therapy still resembles flying blind in that after each cycle complete remission is documented but frequently without taking measurable residual disease (MRD)[17] assessment into account. In addition, more than 50% of relapses are not predicted by MRD assessment and occur in MRD-negative groups.[4] The consequences of this are low levels of test sensitivity of real-time quantitative polymerase chain reaction-based methods,[18,19] whereas flow-cytometry and sequencing-based methods have been characterized by low levels of specificity.[20-22] Thus, MRD assessment during the course of AML treatment is essential and may help to improve clinical research in consolidation therapy of AML. Nevertheless, its assessment is currently only informative for the evaluation of consolidation treatment strategies if MRD is positive and declining or rising. Negative results are still difficult to interpret.[4]

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Therapy-related acute lymphoblastic leukemia

Josep-Maria Ribera

Clinical Hematology Department. ICO-Hospital Germans Trias i Pujol, Josep Carreras Research Institute, Badalona, Universitat Autònoma de Barcelona, Spain

E-mail: jribera@iconcologia.net

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Therapy-related acute lymphoblastic leukemia (t-ALL) refers to ALL developed in patients who have received prior cytotoxic therapies, including chemotherapy and/or radiotherapy for solid or hematologic cancers. In this issue of *Haematologica*, Aldoss *et al.*[1] report the largest retrospective study of patients from a single institution with analysis focused only on cases with prior exposure to cytotoxic therapies. The frequency of t-ALL was 10%, an important subset of patients showed cytogenetic abnormalities similar to those found in therapy-related acute myeloid leukemias (t-AML) or therapy-related myelodysplastic syndromes (t-MDS), and the outcome of t-ALL patients was poorer than that of the *de novo* ALL patients, especially for those who did not undergo allogeneic hematopoietic stem cell transplantation (alloHSCT).

Similar to t-AML or t-MDS, the pathogenesis of t-ALL is attributed to the genotoxic effect of cytotoxic therapies on hematopoietic progenitor cells, but the precise mechanisms are less understood than those of therapy-related myeloid neoplasias. An underlying constitutional predisposition shared by the malignancies and ALL cannot be ruled out, especially for cases with s-ALL. In this sense, some studies have observed a higher prevalence of malignant neoplasms among first-degree relatives of patients with t-ALL or s-ALL. Ten to15% of therapy-related leukemias are t-ALL,[2] and it is frequently confounded with the so-called secondary ALL (s-ALL), that refers to the patients with ALL with antecedent neoplasia but without exposure to cytotoxic therapy. Both t-ALL and s-ALL are infrequent (less than 2%-10% of all ALL cases)[1,3-14] (Table 1), and are unfortunately often considered together in most case series or registry studies. The precise distinction of both types of ALL is important, especially for t-ALL, because prior exposure to cytotoxic therapies could have an impact on both treatment-related morbidity and mortality and on response to chemotherapy and the subsequent use of alloHSCT.[15]

Clinically, t-ALL arises in older patients than *de novo* ALL, and there is a female and white ethnicity preponderance in some series, different to what occurs in newly diagnosed ALL patients. Pediatric cases of t-ALL have also been described.[14] An important question is to know whether t-ALL is biologically different from *de novo* ALL. No significant differences have been reported in the white blood cell (WBC) count, the frequency of central nervous system or other extramedullary infiltration, or in the frequency of the different leukemia phenotypes (T-ALL or B-cell precursor ALL), although some studies have described a lower WBC count in t-ALL patients.[1] However, important differences have been observed regarding genetic background, showing a predominance of high-risk genetic subtypes in t-ALL compared with *de novo* ALL. The most consistent genetic abnormality found across studies is the 11q23 (*KMT2A*) rearrangement, followed by monosomies of chromosomes 5, 7 and/or 17, hypodiploidy, and in some studies, by the Philadelphia (Ph) chromosome (Table 1).[1,2-14,16] Except for the latter rearrangement, these genetic abnormalities are similar to those found in t-AML or in t-MDS and support the etiologic role of prior chemotherapy in the pathogenesis of t-ALL. Alterations of tumor suppressor genes at the 11q23 chromosomal regions may also predispose the cells to both solid and hematological cancers. The 11q23 rearrangements are frequently observed in patients who have received topoisomerase II inhibitors. As occurs in *de novo* Ph-positive ALL, the p190 BCR-ABL subtype is predominant, but the frequency of associated chromosomal abnormalities (ACA, especially monosomies), is higher in cases with Ph-positive t-ALL.[16] Large molecular studies are lacking in t-ALL and, consequently, the frequency of specific subgroups such as the BCR-ABL-*like* is unknown.

Large epidemiological studies have shown that any previous malignancy can lead to an increased incidence of s-ALL or t-ALL, which establishes this ALL as a separate entity.[9,11,12] Among all cancer survivors, those with prior cancer treatment have a higher probability to develop ALL than those with no prior treatment, with this increased risk being observed at any age.[11,12] Regarding the type of previous solid cancer, breast cancer constitutes the most common prior solid malignancy across the series, probably related to its high frequency, the elevated utilization of alkylator and topoisomerase II inhibitors as well as radiotherapy, and the excellent long-term survival for this disease. Lymphomas and other lymphoproliferative disorders encompass the most frequent antecedent of