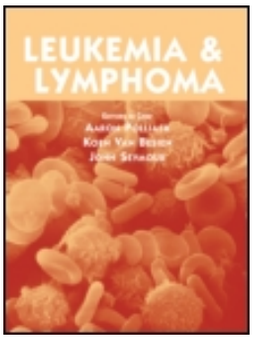

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COMMENTARY

Limitations of targeted therapy with sorafenib in elderly high-risk myelodysplastic syndrome and acute myeloid leukemia

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In contrast to serial improvements in survival outcome for younger patients with acute myeloid leukemia (AML) since the 1970s, minimal gains have been achieved for those over the age of 60 [1]. Clinical outcomes are bleaker still for older patients considered "unfit" for intensive chemotherapy, with the observed median survival only 4 months after low-dose cytarabine (LDAC) [2]. The high unmet need in older patients with AML has propagated clinical investigation of novel therapies alone, or in combination with low-dose chemotherapy. In this issue of ***Leukemia and Lymphoma,*** Macdonald *et al*. examined the multi-kinase inhibitor sorafenib in combination with LDAC in 21 patients over the age of 60 with high-risk myelodysplastic syndrome (MDS) or AML [3]. The maximum tolerated dose from the phase I stage was cytarabine 10 mg twice daily $\times$ 10 days and sorafenib 600 mg daily. Among 20 evaluable patients, the response rate was only 10%, yielding one complete and one partial responder. This study highlights several difficulties hampering the development of targeted therapies in older patient populations.

Although patients over the age of 60 with AML have historically been referred to as elderly and unlikely to benefit from intensive chemotherapy, there is growing acceptance that intensive chemotherapy may confer clinical benefit up to the age of 70 [4]. In clinical trials involving elderly "unfit AML," there is greater emphasis to use objective criteria to define which patients have an unacceptably high early mortality risk from intensive chemotherapy, instead of depending on "physician discretion" [5]. Factors linked to early chemotherapy risk include age $\geq$ 75, Eastern Cooperative Oncology Group (ECOG) performance status $\geq$ 2, complex karyotype and secondary AML with antecedent MDS [5]. In the study by Macdonald *et al*., the reasons that patients were deemed unsuitable for chemotherapy by their physicians were not stated. All 21 patients had ECOG 0–1 performance status, AML karyotype was not available, and nine patients had a prior diagnosis of MDS. To minimize the effect of selection bias and subjectivity in clinical studies, it would be beneficial to have parameters used to define elderly patients "unfit for intensive chemotherapy" incorporated into study inclusion criteria.

The merging of high-risk MDS and AML into clinical trials has been a frequent practice, in part because advanced MDS frequently transforms into AML. However, the increased adoption of demethylating agents for the treatment of high-risk MDS may complicate studies seeking to combine novel therapies with a "standard treatment." For high-risk MDS, combining sorafenib with cytarabine, rather than a demethylating agent makes the pathway to development difficult, as epigenetic modifiers have already demonstrated superior survival outcomes to LDAC in randomized clinical studies [6].

The focus of the study by Macdonald *et al*. was sorafenib, a small molecule inhibitor of Raf, approved by the Food and Drug Administration (FDA) for use in advanced renal cell cancer and hepatocellular carcinoma. In addition to Raf, sorafenib also targets vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR), which likely increases the risk of undesirable side-effects, including the hand–foot skin reaction (HFSR). HFSR has been reported to occur in patients with AML exposed to sorafenib [7]. Interestingly, this complication appears more frequent in pediatric patients, potentially due to higher generated levels of the sorafenib N-oxide metabolite [7]. In contrast, HFSR did not emerge as a complicating feature in the elderly cohort studied by Macdonald *et al*., although the total daily dose of 600 mg daily was lower than that commonly used in other situations. In AML, the primary clinical objective relates to sorafenib's ability to target FLT3-internal tandem duplication (ITD). In a phase I study involving patients with relapsed and refractory FLT3-ITD AML, the overall response rate to single-agent sorafenib was 34% [8]. In combination with chemotherapy in newly diagnosed AML, the overall complete response/complete response with incomplete Blood Count recovery (CR/CRi) rate approaches 100% [9]. The low response rate observed by Macdonald *et al*. may relate to the population studied or

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to potentially suboptimal doses of cytarabine and sorafenib required for tolerability in this elderly patient cohort. The study included 4/21 patients with MDS and 9/21 patients with AML secondary to MDS. Only 3/21 (14%) patients in the study cohort had mutant FLT3-ITD. The frequency of FLT3-ITD in AML appears to peak in young adults, and declines sharply with age to a frequency of 20% in those with AML over the age of 60 [10]. In MDS and secondary AML, the frequency of FLT3-ITD is only 3% and 12%, respectively [11,12]. Although FLT3-ITD is widely considered a poor prognostic factor in adults with AML, the clinical value of targeting FLT3-ITD in elderly patients with AML is contentious. Several studies report no prognostic value for FLT3-ITD in older patients with AML. A larger study involving 243 patients with cytogenetically normal AML treated with intensive chemotherapy suggested that FLT3-ITD significantly worsened survival outcome for those aged 60–69, but not in older individuals [13]. Development of a registration pathway targeting FLT3-ITD in elderly, unfit MDS/AML will therefore be extremely challenging. Although sorafenib may have efficacy in non-FLT3-ITD AML populations, as occurred in one patient in the study by Macdonald *et al.*, indiscriminate exposure of patients to sorafenib would not be appropriate until a reliable biomarker of response can be identified beyond FLT3-ITD.

In contrast to the excellent long-term outcomes observed in patients with CML treated with small molecule inhibitors of BCR–ABL, successful targeting of FLT3 in AML appears to be far more challenging. Although FLT3-ITD appears to represent a *bone fide* driver mutation in AML, clinical studies involving the type II adenosine triphosphate (ATP) small molecule inhibitors sorafenib [14] and AC220 [15] have both demonstrated clinical progression after several months of therapy due to the emergence of drug-resistant mutations affecting either the activation loop D835 or gatekeeper F691 residues. Attempts to improve longer-term responses to FLT3 inhibitors through combination with intensive chemotherapy have also been partly impeded by chemotherapy-induced elevations of circulating FLT3 ligand, which appears to suppress the on-target effects of FLT3 inhibitors [16].

In conclusion, translation of targeted therapy strategies to older populations with AML is complex and should include consideration of (1) which patients are appropriate candidates for non-intensive therapies, (2) whether changing patterns of therapy for MDS may influence which standard agents are combined with novel therapies and (3) the impact of age-specific differences in target frequency, drug metabolism and physiologic tolerance to drugs.

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