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The best laid schemes…

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In this issue of Haematologica[1] Schlenk and colleagues provide a report of results from a clinical trial. The trial was elegantly designed to answer an important question, namely to determine if the addition of a potent and selective FLT3 inhibitor to salvage chemotherapy could improve the rates of response and successful bridging to transplant of patients with relapsed or refractory FLT3-ITD mutated AML.

FLT3-ITD mutated AML is well known to have a generally poor outcome in the setting of treatment with conventional cytotoxic chemotherapy.[2] The regulatory approval of the FLT3 inhibitor midostaurin has improved these outcomes for newly diagnosed patients to a degree,[3] but relapse certainly still occurs. In the relapsed or refractory setting, FLT3-ITD mutations are one of the worst possible prognostic factors,[4] and even the use of potent, selective FLT3 inhibitors such as quizartinib only modestly improve outcomes when used as monotherapy.[5] Therefore, a logical approach is to combine potent, selective FLT3 inhibition with salvage chemotherapy. Randomized trials are required to demonstrate the degree of benefit of this approach, but such trials are difficult to accrue- no one wants to be randomized to the control arm. A 2:1 randomization scheme can sometimes overcome this barrier, but even these trials are still difficult to enroll to completion. Schlenk and colleagues designed a study that had a reasonable chance of attracting participants by allowing all enrollees to receive the combination therapy during the first cycle, with randomization to chemotherapy only versus chemotherapy plus quizartinib reserved for those achieving remission. The response rate would be compared to historical controls using an established statistical method, and the follow up treatment would still provide some crucial randomized data for this combination.

Gilteritinib, another selective, potent FLT3 inhibitor, received regulatory approval for the treatment of relapsed and/or refractory FLT3-mutated AML in the U.S., Europe, and Japan just as this Q-HAM versus HAM trial was getting started. Like the mouse in Robert Burns' poem,[6] the investigators planned their scheme well but for the approval of gilteritinib.[7] With the availability of a simple, effective oral therapy for relapsed/refractory FLT3-mutated AML,[8] patients and clinicians voted with their feet and accrual to the Q-HAM v HAM trial ground to a halt.

Only 11 patients were randomized when the study was stopped. Out of the 11 patients, 6 achieved a response, several made it to allo-transplant, and there were a few long-term survivors. The tiny group of pts actually had a median survival of about a year (double the QuANTUM-R results[5]). These results, even though statistically weak, still proved a glimpse, almost like that of a pilot study, into this combination. We can never know when it might be appropriate to study a combination of quizartinib and this salvage regimen in the future, and so we should not be quick to discard any data, even if derived from so small a sample.

How many times have clinical investigators enrolled patients on studies only to never see any follow up? If a trial is negative or doesn't accrue, there is apparently insufficient academic glory to induce the investigators to put together the data and publish, which is why Schlenk and colleagues are to be lauded for providing what they had. Their trial design was novel and could provide a spark of imagination for future trial designers.

The phenomenon of a new regulatory approval interfering with ongoing clinical studies is likely to be more and more common, as drug approvals in AML have increased seemingly exponentially.[9] To paraphrase Burns, the best laid schemes of mice and leukemia researchers often fall apart. That doesn't mean the results should be plowed over and remain forever buried.

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