Hematopoietic cell transplantation soon after first relapse in acute myeloid leukemia – the PROS

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"When the facts change, I change my mind. What do you do, sir?" - John Maynard Keynes

More than 40 years ago, Appelbaum and colleagues suggested the best time to do an allogenic hematopoietic cell transplant in people with acute myeloid leukemia (AML) not transplanted in first histological complete remission is as soon as possible after they relapse.[1] Their suggestion was based on several considerations, including the loss of transplant candidates from adverse events caused by trying to achieve a second histological complete remission pretransplant.[2]

Since then, there have been important advances in the range of acceptable donors, pretransplant conditioning regimens, prevention of graft-*versus*-host disease (GvHD), and supportive care which have improved safety and efficacy of allotransplants in people with AML in remission or not.[3-5] Large retrospective analyses and recent observational data from the Center for International Blood and Marrow Transplant Research (CIBMTR) report better outcomes in people receiving transplants in second histological complete remission compared to those transplanted not in remission.[5-10] However, these data do not address whether pretransplant intensive re-induction chemotherapy improves survival of people who relapse, and do not account for people receiving re-induction therapy but not proceeding to transplant for diverse reasons, such as toxicities precluding a transplant, withdrawal of consent, and death. Additionally, these data do not distinguish people transplanted in untreated first relapse from those receiving a transplant after failed attempted reinduction or from those never achieving a first histological complete remission. Also, many studies focus on point-estimates of outcomes without reporting confidence intervals, which are often huge.[11]

Despite these considerations, most transplant centers request achieving a second complete histological or measurable residual disease (MRD)-negative status before advancing to a transplant.[12-16] Transplants in untreated first relapse are rarely considered or mentioned. Consequently, most people transplanted in relapse failed re-induction and increasing numbers are transplanted in second complete remission.[6-10] Comparing outcomes of these cohorts obviously ignores strong selection biases.

Several factors likely account for this practice and influence current expert recommendations and clinical practice guidelines. We previously reported our view of consensus guidelines.[17,18] Physicians and/or patients may choose to not

Burning of the Templars, 1314. Workshop of Virgil Master. This file has been provided by the British Library from its digital collections. It is also made available on a British Library website. Catalogue entry: Royal MS 20 C vii. Detail of a miniature of the burning of the Grand Master of the Templars and another Templar. From the Chroniques de France ou de St Denis, BL Royal MS 20 C vii f. 48r.

risk toxicities and potential death from a transplant when the likelihood of long-term survival is low even when the outcome is better compared with the alternatives. Other physicians use re-induction therapy to assess disease sensitivity and likelihood of cure with a transplant. The many people receiving a transplant after failing re-induction therapy suggests many advance to a transplant anyway. Notably, the toxicities of re-induction therapy and of transplants are cumulative or even synergistic. Public reporting of center-specific outcomes also influences physicians' selection of people with the best predicted transplant outcome like what is reported in cardio-thoracic surgery and kidney transplantation.[19-21] The perception that transplanting the best candidates results in better outcomes ignores results of the multi-variable analyses used to predict expected outcomes which attempt to account for known adverse risk co-variates. Conversely, some subject- and transplant-related co-variates like frailty, socio-economic status, and MRD are neglected in the analyses.[22] These issues have contributed to the incorrect conclusion and recommendation that there is a need for re-induction therapy pretransplant.

The recently published phase III ETAL-3-ASAP trial addresses the efficacy of pretransplant re-induction therapy on transplant outcomes.[23] The authors reported no benefit but longer hospitalization and more adverse events in the re-induction cohort.

Most data we reviewed support a transplant as soon as reasonably possible after relapse without attempting pre-transplant re-induction. Co-variates which might identify people likely to achieve a histological complete response after re-induction therapy such as long duration of first remission, favorable cytogenetics, low ECOG performance score, and low blood myeloblast concentration do not help decide which people might benefit from post-relapse therapy because they also identify patients who are likely to have favorable outcomes when transplanted in relapse.[5,14,24] Response to pretransplant re-induction therapy identifies people with more responsive disease. As such, it is a predictive co-variate or biomarker for a better transplant outcome. This is best viewed as an association, not cause-and-effect.

We are not suggesting everyone with AML in first complete remission who relapses goes directly to a transplant. This decision must be made on an individual basis. For people with a brief first histological complete remission or with other adverse risk co-variates, and older people with important co-morbidities, decision-making is complex. However, in many people, advancing to a transplant without further therapy is reasonable. And any decision should consider the proposed transplant conditioning regimen.

In conclusion, we suggest the current practice of giving everyone with AML who relapses pretransplant re-induction therapy is without a strong scientific basis and likely to cause more harm than benefit. Others have also reached similar conclusions.[25]

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Contributions

EC and RG wrote the manuscript.

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