Historical Controls?

As noted by Gökbuget and colleagues,[1] licensing agencies increasingly depend on the results of single arm phase II trials.[2] As attention focuses on small, molecularly defined, patient subsets, urgent clinical need, and eagerness to test scientifically compelling targeted agents encourage us to rely increasingly on historical controls.[3] However, historical, sometimes ad hoc, outcomes are likely less favorable than those of contemporary patients treated on formal clinical trials.

Gökbuget and colleagues define relapse "by standard criteria" as return of leukemia after a complete remission. What are the contemporary standard criteria? In the past, marrow relapse required marrow blasts ≥ 25%. WHO requires > 20% blasts in the marrow, or peripherally, in order to establish acute lymphoblastic leukemia.[4] A recent phase II blinatumomab trial accepted patients with ≥ 10% marrow blasts,[5] and a recent phase II inotuzumab trial enrolled patients with marrow blasts ≥ 5%.[6] Neither flow cytometric nor molecular confirmation is noted. In another paper, Gökbuget and colleagues compare the results of the blinatumomab trial, which required marrow blasts ≥ 10%, to the international reference data that required 'conventional' relapse.[7] Historic benchmarks derived from populations with marrow blasts ≥ 25% may not serve for comparison with cohorts with lesser marrow involvement.

Furthermore, the data presented by Gökbuget and colleagues[1] derive from 1706 patients who enrolled in a clinical trial at diagnosis and then relapsed. Their subsequent courses were tracked through salvage therapies and subsequent relapses. Only a few were treated with only palliative intent. Substantial numbers allow for useful subgroup analyses. However, patients may or may not have been enrolled in subsequent formal clinical trials.

Ad hoc patients may differ from patients who enroll in phase II trials, and must meet performance status, organ system, and freedom from infection requirements. In addition, a patient elects to enroll in a clinical trial. Kirby and colleagues reviewed 102 patients who received conventional therapy for malignant glioma. Forty-eight percent of patients met eligibility requirements for a one-vessel intra-arterial treatment study and lived longer than ineligible patients (18.4 *vs.* 5.1 months, $P<0.00001$). Seventy-three percent of patients met eligibility requirements for two-vessel intra-arterial treatment study and lived longer than ineligible patients (14.8 *vs.* 3.5 months, $P<0.00001$). Thirty percent of patients met eligibility requirements for middle cerebral artery treatment study, and survival was more similar to that of ineligible patients (13.6 and 9.9 months).[8] Outcomes may differ between patients meeting eligibility requirements and those who do not. Outcomes may also differ between patients who elect to enroll in clinical trials and those who refuse.

As discussed by Gökbuget and colleagues,[1] outcomes are slowly improving over time, despite a previous lack of novel treatment strategies. Therefore, an eligible patient who elects to enroll in a formal clinical trial tomorrow is likely to have a superior outcome compared to a patient who relapsed 5 or 10 years ago and received ad hoc salvage therapy. Are the authors able to compare outcomes of patients treated ad hoc and those treated in formal trials? Sadly, my colleagues and I are unable to do so in our Therapeutic Advances in Childhood Leukemia (TACL) database.[9,10]

Properly constructed historic controls are crucial to our attempts to move forward. However, identifiable biases work uniformly against the "historical" control, and they may exaggerate the benefit of candidate interventions. The magnitude of such bias may be significant and is unknown to me.

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