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EDITORIAL

Acute myeloid leukemia

New drugs in AML: uses and abuses

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So, the last will be first, and the first will be last.

Mathew 20:16

Many persons with acute myeloid leukemia (AML) are excluded from new drug studies for diverse reasons such as a poor performance score, abnormal kidney, liver or heart function, infection with hepatitis or human immune deficiency-related viruses, tests performed outside narrow-specified time intervals, co-morbidities, frailty, or a prior cancer even when risk of recurrence is extremely low [1]. These exclusions drastically limit clinical trials eligibility, especially in older persons, given the 65–70-year median age of diagnosis. For example, the risk of having a non-fatal solid neoplasm by the age 70 is >20%, with an annual rate of 1.5% [2].

Research into exclusions from oncology clinical trials has focused almost exclusively on persons with solid neoplasms [3]. A recent US Food and Drug Administration (FDA) study reported that 63% of 284 commercial investigational new drug (IND) applications for cancer in adults in 2015 limited eligibility to subjects with an Eastern Cooperative Oncology Group (ECOG) performance score <2. Only 1% allowed the enrollment of subjects with an ECOG performance score of 3 [4]. Similarly, data from the Kaiser Permanente Practice Group estimated that 61% of >12,000 persons with breast, lung, or colorectal cancers would be excluded from the typical clinical trials in these diseases [5].

A subtler but more common bias operates when otherwise-eligible persons are not even considered for a clinical trial, often because of the perception that they would be a poor study candidate. Unfortunately, most studies do not report the number of persons screened, enrolled, or excluded as a proportion of eligible persons; and this does not include the large numbers of subjects never screened or referred to a study site. For example, in the United States, 60% of persons >66 years with AML receive no therapy within 3 months of diagnosis [6]. On the basis of these considerations, we estimate that <10% and probably <5% of persons with AML enter the clinical trials, a rate similar to solid neoplasms. It would be naive not to suspect excluding subjects from the trials reflects a desire to make the results look as good as possible, thereby increasing the likelihood of health authority approval and/or publication, although these exclusions are understandable in view of the time, effort, and costs of drug development,

Although our first issue involves systemic, unquantified selection biases, the second, ironically, is unrestricted use of drugs post approval. Some of the fault rests with the health authorities [7]. For example, although the trial leading to FDA approval of midostaurin enrolled only subjects <60 years, approval is for all adults with an *FLT3* mutation, including those >60 years, where the risk/benefit ratio of midostaurin is unstudied [8] (https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/207997s000lbl.pdf). Although *FLT3* mutations are less common in people aged >60 years compared with younger persons (15% vs. 25%), most persons with AML are >60 years [9–11]. Consequently, considerable use of midostaurin will likely occur in this untested setting. Similarly, although the trial reporting a survival advantage for CPX-351 over conventional cytarabine and daunorubicin enrolled only subjects 60–75 years with secondary AML, the FDA approval has no age restriction [12, 13] (https://www.fda.gov/Drugs/Informa

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tionOnDrugs/ApprovedDrugs/ucm569950.htm). We anticipate widespread CPX-351 use in the unstudied group of younger AML persons, while noting that defining a case of AML as secondary is necessarily probabilistic and often inaccurate [14].

Current drug approval policies are thusly problematic because: (1) they do not quantify the effects of selection biases in the trials on which the approval is based [1, 15]; and (2) they grant de facto approval in clinical settings in which the drug was not tested for safety or efficacy, ignoring the likelihood that the drug will be used in these settings. Given the shortcoming of post-approval surveillance mechanisms, it is highly unlikely that unfavorable outcomes would be reported at all or with as much publicity accompanying the trial(s) on which the approval was based.

How to solve these problems? Our proposal

(1) Require advanced phase clinical trial reports to indicate the number of randomized or treated subjects as a proportion of those screened and/or potentially eligible for the trial. The proportion of all the subjects in each category (for example, >60 years) seen in the trial center, but ineligible should also be noted and the reason(s) for exclusion should be specified. Enforcement mechanisms would likely be needed, such as a commitment to report these data when a trial is registered on www.clinicaltrials.gov, a requirement by a health authority, and/or funding agency when the trial is reviewed, or by a journal when a typescript is submitted for publication. Concomitant with this recommendation would be the requirements to support screening ascertainment by the groups funding such studies, recognizing the ability to assess the screened, but excluded, populations has been shown in basket-like trials [16]. Although a step forward, we acknowledge that this action will not correct the bias of non-referral to a trials center.

(2) Broaden the eligibility criteria once safety is estimated from early phase trial data in persons selected to avoid confounding effects of co-morbidities. The influence of such trials has been questioned by Statler et al., who found no association between a drug's toxicity profile in early-phase studies or based on the drug's known mechanism of action or pharamaco-kinetics/-dynamics and subsequent eligibility criteria in 97 randomized trials in hematologic neoplasms (33% in leukemia; 78% phase-3) [17]. They also noted no association between organ function eligibility criteria and subsequent organ toxicity. Analyses of 13 Southwest Oncology Group (SWOG) leukemia studies reported that 10% of almost 2500 subjects enrolled and treated in these studies were found retrospectively to be ineligible [18]. However, eligible and excluded subjects had similar frequencies of adverse events, remission rates, and survival. Several eligibility criteria could readily be modified, even in early-phase studies. For example, although most AML studies require a bone marrow examination immediately pre-study, there are no convincing data results that would be meaningfully different compared with an examination done 1 or 2 months earlier. Further, although trials frequently exclude persons with a prior cancer (other than non-melanoma skin cancers or similar non-invasive cancers), this makes little sense given the 1–2% annual risk of developing a second cancer in persons with AML >65 years, with survival in many of these cancers exceeding that of older adults with AML [2]. Moreover, outcomes of AML therapy are similar in persons who have received only surgery and/or radiation for cancer, but not chemotherapy, as in patients without a prior cancer diagnosis, when adjusted for other prognostic and predictive variables [19].

Building on these observations, Montalban-Bravo et al. reported an innovative phase-2 study of 109 subjects with AML or MDS ineligible for standard trials for the aforementioned reasons [20]. The study was designed to stop if the 50% 60-day survival rate for similar subjects not treated on a protocol was exceeded. This did not occur. Within the sample size limits, survival was not affected by co-morbidities that included hepatic or renal impairment, and even concomitant invasive non-myeloid cancers. Thirty-five percent of subjects had grade-3/-4 non-hematologic toxicity, about one-half of which were febrile neutropenia or vomiting, rates like eligible subjects in similar studies.

Despite these data and the inaccuracy in predicting the outcomes in persons with AML [21], we readily acknowledge that persons with a performance score of 3 are very likely at greater risk of therapy-related death than more fit persons. Nonetheless, when prognosis with standard therapy is poor, an unfit person might be keen to participate in a clinical trial. Joffe and Fernandez-Lynch note that the efforts to legalize *right-to-try* initiatives are superfluous because the FDA already approves virtually all expanded access requests and that these initiatives are potentially dangerous if FDA oversight is removed [22]. Once early phase testing is complete, we recommend including typically ineligible subjects in future studies, perhaps as a separate stratum, because this would permit more rigorous data collection and analyses and better reflect that population who will ultimately be treated with these drugs (if approved) than a *right-to-try* policy.

One downside to enrolling currently ineligible subjects in clinical trials is the potential that doing so would worsen the results and decrease the likelihood of drug approvals. This argument is specious. In practice, we want to know the outcomes in persons most likely to receive the drug. Furthermore, this claim ignores the fundamental purpose of clinical trials; namely, to provide new therapies as quickly as possible to a broad population of persons in whom

benefit/risk ratios are higher with the new therapy. Focusing only on approval defeats, this purpose, while potentially offering false hope to the many people deemed ineligible for the trial.

(3) *Encourage* formal follow-up studies in persons excluded from a pivotal trial(s) of a new therapy who later receive that therapy. Post-marketing phase-4 studies with relaxed eligibility criteria are of relatively little scientific value, often incomplete, and/or unreported. We emphasize "encourage", recognizing it is unlikely our view that will prevail unless FDA enforces our suggestions.

In summary, we think most persons with AML are excluded from most clinical trials. Although the reasons for these exclusions are often not scientifically founded, the exclusions mean that the answers generated from these trials may not apply to most persons with AML, including the subset for whom the approval is granted. Beyond this, health authority approvals and subsequent use of drugs should be limited to settings in which the drug(s) was tested and found to be safe and efficacious. We suggest ways to address these important issues. While acknowledging adoption of our proposals is unlikely, hope springs eternal.

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