EDITORIAL

New drug approvals in acute myeloid leukemia: what’s the best end point?

Leukemia (2016) 30, 521–525; doi:10.1038/leu.2015.262; published online 18 December 2015

If a man will begin with certainties, he shall end in doubts, but if he will be content to begin with doubts, he shall end in certainties—Francis Bacon

The US Food and Drug Administration requires proof of clinical benefit before granting approval to new drugs for treatment of neoplasms such as acute myeloid leukemia (AML). Clinical benefit, in this context, is defined as improvement in length and/or quality-of-life (QoL) or in validated surrogates for these end points.1 Although several drugs have been approved in the last 3 years for other leukemias including chronic myeloid leukemia, chronic lymphocytic leukemia and acute lymphoblastic leukemia, new drug approvals for AML have lagged. The overwhelming reason is failure to develop new, effective AML therapies. We cannot identify a drug whose Food and Drug Administration approval would have markedly changed the prognosis of most persons with AML. Nonetheless, some AML experts believe a greater emphasis on end points other than survival would facilitate drug development and approvals in AML. We discuss pros and cons of other potential end points for trials of new drugs for AML in light of distinctive disease characteristics, which complicate straightforward consideration of end points. An example is the demanding nature of AML therapy raising questions, particularly in older persons, about the magnitude of better survival and the proportion of persons benefiting needed to justify this demand. Other considerations include the efficacy of rescue (salvage) therapies after failure of initial therapy, especially allogeneic hematopoietic cell transplants and improvements in prevention and treatment of fungal and other infections, important causes of death in persons with AML.2–4 These rescue strategies and improvements in supportive care act to dissociate survival after AML therapy from surrogates such as event-free survival (EFS). Moreover, efficient access to blood and bone marrow samples allows identification of many cytogenetic and molecular subgroups of AML and provides sensitive, albeit imperfect ways to quantify residual leukemia cells in persons in histological complete remission. These developments raise the possibility of approving a new drug in only a subset of persons with AML and/or of using measurable residual disease (MRD) testing as a surrogate end point.5,6 However, despite these many advances and considerations we conclude no current end point for approving drugs in AML is entirely satisfactory.

CONVENTIONAL SURROGATES FOR SURVIVAL: COMPLETE REMISSION, REMISSION DURATION AND EFS

The use of a survival end point for drug approval in AML requires following subjects for a sufficient interval for a substantial number of events (deaths) to occur for a precise estimate. In older people with AML on clinical trials probability of survival is 25–30% at 2 years and it is considerably higher in younger persons.7–9 Consequently, it may take 2–3 years or more to accurately predict survival. This delay has resulted in interest in a surrogate end point for survival. If a surrogate can be assessed more quickly or has a faster event rate than death, trials using a surrogate end point can be done more quickly. However, a valid surrogate must correlate with survival such that improvement in one accurately predicts improvement in the other.10–12

The most obvious survival surrogate in AML is complete remission usually defined as < 5% bone marrow blasts and more than 1 x 10E+9/l granulocytes and more than 100 x 10E+9/l platelets in the blood. Validity of this surrogate is based on the observation persons achieving complete remission live longer than those who do not, a prolongation reflecting the interval in complete remission.1,13 In prior studies survival after relapse was similar to that of persons never achieving remission (a situation now changed; see below), suggesting longer survival associated with complete remission reflects achieving a state of complete remission rather than an association between achieving complete remission and general health or AML biology.13 However, although complete remission is a more tractable end point than survival, data from several recent studies of new AML drugs report increased complete remission rates compared with controls but no increase in survival implying a disassociation under some conditions.14,15

If complete remission is an imperfect surrogate for survival, it seems unlikely less stringent responses such as complete remission without platelet recovery (CRp) or complete remission without hematologic recovery (Cri) will be more valid survival surrogates. Empiric data are conflicting. Walter et al.16 reported persons receiving intensive anti-leukemia therapy (conventional or high-dose cytarabine with or without an anthracycline) lived longer if they attained complete remission rather than CRp after accounting for covariates such as cytogenetics and lead-time bias. In contrast, data from older persons receiving less intensive therapy such as azacitidine suggest no survival difference between subjects achieving complete remission compared with subjects achieving other responses including partial remission.17,18 These contradictory data suggest the association between complete remission or other response states and survival differs for age cohorts and for different drugs.

EFS is sometimes considered a surrogate for survival. (In fact, survival is an EFS end point where death is the event; see below.) Its analog, progression-free survival, is the basis for many new drug approvals in other neoplasms.19,20 In contrast to survival where death is the only event of interest, EFS also includes failure to obtain complete remission and relapse from complete remission. As most failed remission attempts and relapses in persons achieving complete remission occur within 1 year of starting therapy, EFS is quicker to evaluate than survival.21,22 Another advantage of EFS is a more precise test of a drug’s efficacy than survival. This is because persons with AML can live for a considerable interval after events (such as relapse) because of rescue therapies and supportive care discussed above.2–4 These post-relapse interventions are often unspecified in the design of phase-2 and -3 studies and may be used in non-random and biased ways, the consequence of which is to convert a controlled study into an observational database of uncontrolled interventions.23 Accordingly, if management of people after therapy failure differs between the conventional and investigational treatment arms of a randomized trial, survival may differ...
NEWER SURROGATES: MRD AND BRIDGE TO TRANSPLANT

In many neoplasms, follow-up after therapy is indirect relying predominantly on radiologic assessment such as computer tomography, magnetic resonance imaging or positron emission tomography. In contrast, in AML the ability to easily access blood and bone marrow samples is direct and has resulted in the development of sensitive techniques to evaluate MRD including multi-parameter flow cytometry (MPFC), PCR, analyses of genes and gene expression and proteomic analyses. PCR and especially MPFC have found widest application. Considerable data indicate results of MPFC and PCR testing for MRD allows stratification of persons with AML in histological complete remission into cohorts with very different risks of relapse, EFS and survival.

Although counterintuitive, incorporating a requirement for a negative MRD test in the definition of complete remission or of EFS might decrease the strength of the correlation between these end points and survival. If relapse was said to occur if there was a positive MRD test despite having < 5% blasts histologically, EFS in such persons would shorten, although by histological criteria they would remain in complete remission. However, if physicians acting on this new criterion chose to intervene (for example, with an allotransplant), survival might increase. This would have the effect of decreasing the strength of the correlation between EFS and survival unless physicians intervene with therapies that shorten survival. This is more than a theoretical possibility where MRD replaces histology as the definier of relapse given non-trivial rates of false negativity and positivity of MRD testing (discussed below).

Survival data are typically reported in terms of medians. However an improvement in long-term survival may not be detected as an increase in median survival if less than one-half of persons benefit from an intervention. There is a very low risk of AML relapse in persons in complete remission for 3 or more years regardless of prior prognostic cohort. These data suggest 3-year leukemia-free survival might be a reasonable surrogate for long-term survival. For example, Sargent et al. reported freedom-from-progression at 30 months in persons with follicular lymphoma was a valid surrogate for long-term progression-free survival (median more than 7 years). In persons with AML, Walter et al. reported a strong correlation between achieving complete remission and survival at 3 years. A stronger correlation with long-term, if not median, survival might result by considering results of MRD testing in the definitions of complete remission or EFS.

For example, a higher proportion of persons might be alive at 3 years if they achieve complete remission with a negative rather than with a positive MRD test. Alternatively, a higher proportion might be alive at this time if they remain in complete remission with a negative MRD test at, for example, 3, 6 or 12 months equivalent to EFS with a negative MRD test at these time points.

Accuracy of MRD testing as a predictor of relapse in persons with AML is controversial. Specifically, its precision in separating cohorts more and less likely to relapse, contrasts with imprecision in predicting relapse at the subject level. For example, in SWOG study SO106 Othus et al. recently reported MPFC test results at the time of complete remission was a stronger predictor of relapse-free survival (relapse and death as events) than age, pre-treatment death from co-morbidities frailty, or therapy related adverse events compete with events such as death from resistant AML. Such competing risks interfere with and/or preclude a precise estimate of events of primary interest such as efficacy of a new anti-leukemia therapy, reduce statistical power and lead to inferential error. Although a complete discussion of the limitations of using a composite end point such as EFS in AML is beyond the scope of our commentary, this is an important unresolved issue.
cytogenetics or NPM1 and FLT3 mutations. However, the univariate c-statistic for the MPFC results in complete remission to predict relapse-free survival was only 0.58 (1.0 = perfect prediction; 0.5 = no predictive value). The c-statistic value for relapse-free survival prediction of a multivariable model incorporating all these features was only about 0.7. However, this study used MPFC techniques developed 5–10 years ago; more sophisticated MPFC testing is now available but has not been validated as being more sensitive and/or specific correlate of relapse or relapse-free survival. Should MRD testing results become sufficiently accurate such that complete remission with a negative MRD test reproducibly identifies long-term survivors, this outcome or EFS with a negative MRD test might be reasonable end points for new drug approvals. Elsewhere we discuss substantial theoretical and practical limitations of MRD testing in AML, a situation that differs enormously from MRD testing in other leukemias such as acute lymphoblastic leukemia and chronic lymphocytic leukemia, where the testing target is lineage marker (IGH or TCR rearrangement) rather than neoplasm specific. Furthermore, even in a disease such as chronic myeloid leukemia where there is a highly sensitive and specific marker of the leukemia clone (BCR/ABL) there is a >50% rate of false negative PCR tests when used to predict cure. These data suggest caution using results of MRD testing as a survival surrogate regardless of potential technical advances.

Acceptance of these surrogate end points such as complete remission with a negative MRD test at a pre-specified time point requires standardization of MRD testing. It will require agreement about what constitutes long-term survival and how strongly correlated the surrogate end point must be, the former preferably empirically derived as suggested above and the latter perhaps guided by the c-statistic. More focus on identifying surrogates for long-term survival might comport with observations most people with AML are more interested in whether they will be cured than whether they will live 3 months longer even if such an increase were statistically significant. The example of interleukin-2 therapy in kidney cancer provides precedent for Food and Drug Administration approval of new drugs when median survival is not prolonged but where long-term remissions occur in some people.44

Recently there is interest in whether a new drug might increase the proportion of persons able to proceed to an allotransplant. Fundamental to using this end point, commonly termed bridge to transplant in new drug approvals is the notion this end point will correlate with survival. A strong correlation is unlikely for several reasons. For example, the definition of who is able to receive a transplant is subjective, inconsistent and non-reproducible. Persons in studies using a bridge to transplant end point frequently only attain CRp or CRI pretransplant. As discussed, it is unclear if these response states are associated with a survival advantage.53 CRi and CRp are more frequently associated with a positive MRD test than is conventional complete remission and thus may be associated with a higher risk of relapse post transplant and worse survival.44 Moreover, post-transplant outcomes such as graft-versus-host disease and cytomegalovirus infections complicate analyses of EFS or survival with the bridge to transplant approach. For example, what if a therapy given as a bridge to transplant produces a high rate of CRi and CRp responses but increases likelihoods of death from graft-versus-host disease or cytomegalovirus pneumonia? What is needed is a randomized trial where conventional therapy and bridge to transplant strategies are compared for survival outcomes and that proves moving to a transplant improves survival over a non-transplant strategy in persons with similar response to the new drug. No such studies are reported nor likely to be done. Subjects are removed from phase-2 studies to receive a transplant because it is felt that they are likely to fare poorly otherwise. However, this action is a form of informative censoring that violates the assumption of non-informative censoring inherent to Kaplan–Meier survival analyses.45 On the basis of the sum of these considerations we consider bridge to transplant an unvalidated end point that should not be used for new drug approvals. It assumes shifting to a transplant that improves survival but it may also miss efficacy of a new drug if transplant outcomes are unfavorable.

**CLINICAL BENEFIT ASSESSED BY QOL INSTRUMENTS**

Improvement of QoL is a worthy objective in AML given the morbidity (including frequent transfusions and hospitalizations) and mortality associated with AML therapies, which often result in relatively small gains in survival for most people. Although better QoL is an explicit Food and Drug Administration criterion for new drug approval, the relation between complete remission or EFS, each with or without a negative MRD test, and better QoL is poorly studied.1,46 Nonetheless, most clinicians believe there is a strong association because persons achieving and maintaining complete remission are typically happier and fitter than those failing to do so. It is plausible and testable achieving and remaining in complete remission confers readily quantifiable benefits that improve QoL even if survival is unchanged. Among these benefits are the possibility of receiving fewer transfusions and drugs and spending less time in medical facilities. These variables as well as QoL are influenced by disease state (complete remission or not), continued chemotherapy or a recent transplant. Differences in QoL may depend on a person’s response state (complete remission, CRp and CRI) and response duration and might only become apparent after recovering from the adverse effects of anti-leukemia therapy. These hypotheses need testing. Studies that carefully measure QoL over time are critical to provide data needed to define criteria for non-survival clinical benefits provided by AML therapies.

In summary, defining clinical benefit of therapy in AML trials is complicated by several disease- and treatment-specific considerations and statistical constraints that make survival a challenging and perhaps inappropriate end point for new drug approvals. Although conventional complete remission and EFS end points do not correlate well with survival, EFS may be a better assessment of a new drug’s efficacy because it is unaffected by subsequent uncontrolled, potentially biased interventions. Complete remission, EFS or both may correlate with better QoL. Assuming MRD assessment becomes more accurate, which it may not, it may be possible to introduce complete remission or EFS with a negative MRD test as surrogates for long-term survival in the future but this is premature. Much work is needed to test these hypotheses. If we discover a knockout drug for AML many of these considerations may become unnecessary. To paraphrase what Supreme Court Justice Potter Stewart said regarding obscenity: ‘I cannot define obscenity but I know it when I see it’. We will know a really effective AML drug when we see it!

We hope our commentary stimulates consideration of alternative end points for approval of new drugs for AML, especially for so-called targeted therapies under development. More importantly, we hope this discussion stimulates collection and analysis of data required to support end points other than survival for approval of new drugs in AML. To return to Francis Bacon’s comment: ‘If a man will begin with certainties, he shall end in doubts; but if he will be content to begin with doubts, he shall end in certainties’. We are certain about the former but less so about the latter.

**CONFLICT OF INTEREST**

RPG is associated with Celgene Corp. His opinions are his own and not necessarily those of Celgene Corp.
REFERENCES

1. Appelbaum FR, Rosenblum D, Arcieri RJ, Carroll WL, Breitfeld PP, Forman SJ et al. Endpoints to establish the efficacy of new agents in the treatment of acute leukemia. Blood 2007; 109: 1810–1816.

2. Burnett A, Goldstone A, Hills R, Milligan D, Prentice A, Yin J et al. Curability of patients with acute myeloid leukemia who did NOT undergo transplantation in first remission. J Clin Oncol 2013; 31: 1293–1301.

3. Cornely OA, Maertens J, Winston DJ, Perfect J, Ullmann AJ, Walsh TJ et al. Posaconazole vs fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med 2007; 356: 348–359.

4. Pagano L, Caira M, Cardoni A, Aversa F, Castagnola C, Caramatti C et al. Evaluation of the practice of antifungal prophylaxis use in patients with newly diagnosed acute myeloid leukemia: results from the SEIFEM 2010-18 registry. Clin Infect Dis 2012; 55: 1515–1521.

5. Estey E, Levine R, Löwenberg B. Current challenges in clinical development of targeted therapies: the case of acute myeloid leukemia. Blood 2015; 125: 2461–2466.

6. Goldman JM, Gale RP. What does MRD in leukemia really mean? Leukemia 2014; 28: 1131.

7. Löwenberg B, Ossenkoppele GJ, van Putten W, Schouten HC, Graux C, Ferrant A et al. High-dose daunorubicin in older patients with acute myeloid leukemia. N Engl J Med 2009; 361: 1235–1248.

8. Rand S, Othus M, Godwin JE, Willman CL, Norwood TH, Howard DS et al. A phase 2 trial of azacitidine and gemtuzumab ozogamicin therapy in older patients with acute myeloid leukemia. Blood 2013; 122: 3432–3439.

9. Burnett AK, Russell NH, Hills RK, Hunter AE, Kjeldsen J, Yin J et al. Optimization of chemotherapy for younger patients with acute myeloid leukemia: results of the Medical Research Council AML15 trial. J Clin Oncol 2013; 31: 3360–3368.

10. Prentice RL. Surrogate endpoints in clinical trials: definition and operational criteria. Stat Med 1989; 8: 431–440.

11. Buyse M, Molenberghs G, Burzykowski T, Renard D, Geys H. The validation of surrogate endpoints in meta-analyses of randomized experiments. Biostatistics 2000; 1: 49–67.

12. Buyse M, Molenberghs G. Criteria for the validation of surrogate endpoints in randomized experiments. Biometrics 1998; 54: 1014.

13. Freireich EJ, Gehan EA, Sullman D, Boggis DR, Frei E 3rd. The effect of chemotherapy on acute leukemia in the human. J Chronic Dis 1961; 14: 593–608.

14. Burnett AK, Russell NH, Hunter AE, Milligan D, Knapper S, Wheatley K et al. Clofarabine doubles the remission rate in older patients with acute myeloid leukemia but does not improve survival. Blood 2013; 122: 1384–1394.

15. Burnett AK, Hills RK, Hunter AE, Milligan D, Kell WJ, Wheatley K et al. The addition of gemtuzumab ozogamicin to low-dose Ara-C improves remission rate but does not significantly prolong survival in older patients with acute myeloid leukemia: results from the LRF AML14 and NCRI AML16 pick-a-winner comparison. Leukaemia 2013; 27: 75–81.

16. Walter RB, Kantarjian HM, Huang X, Pierce SA, Sun Z et al. Effect of complete remission and responses less than complete remission on survival in acute myeloid leukemia: a combined Eastern Oncology Group, Southwest Oncology Group, and MD Anderson Cancer Center Study. J Clin Oncol 2010; 28: 1766–1771.

17. Theop S, Izytkson R, Seegers V, Recher C, Raffoux E, Quinonel B et al. Azacitidine in untreated acute myeloid leukemia: a report on 149 patients. Am J Hematol 2014; 89: 410–416.

18. Pleyer L, Burgstaller S, Girschikofsky M, Linkesch W, Stauder R, Pfeilstocker M et al. Azacitidine in 302 patients with WHO-defined acute myeloid leukemia: results from the Austrian azacitidine registry of the AGMT-study group. Ann Hematol 2014; 93: 1825–1838.

19. Herndon TM, Demko SG, Jiang X, He K, Gootenbeek JE, Cohen MH et al. US Food and Drug Administration approval: Peginterferon-alfa-2b for the adjuvant treatment of patients with melanoma. Oncologist 2012; 17: 1323–1328.

20. André T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T et al. Potential cure of acute myeloid leukemia: analysis of 1069 patients in first complete remission. Cancer 2007; 110: 2756–2760.

21. Hernán MA, Hernandez-Diaz S, Robins JM. Randomized trials analyzed as observational studies. Ann Intern Med 2013; 159: 560–562.

22. Walter RB, Othus M, Paietta EM, Hernandez HF, Lee J-W, Sun Z et al. Effect of genetic profiling on prediction of therapeutic resistance and survival in adult acute myeloid leukemia. Leukemia 2015; 29: 2104–2107.

23. Othus M, van Putten W, Löwenberg B, Petersdorf S, Rand S, Erba H et al. Relation between event-free survival and overall survival in acute myeloid leukemia: a report from SWOG, HOVN/SAKK, and MRC/NCRIL (Submitted).

24. Harrell Jr., Frank E. Regression modeling strategies. Springer: New York, NY, USA, 2001.

25. Oakes D. Semiparametric inference in a model for association in bivariate survival data. Biometrika 1986; 73: 353–361.

26. Luskin MR, Lee J-W, Fernandez HF, Lazarus H, Rowe J, Tallman M et al. Results of the ECOG E1910 trial in younger adults with AML using an event free survival endpoint are concordant with results based on overall survival: potential for a surrogate endpoint to facilitate rapid approval of therapies in AML. Blood 2014; 124: 2599 (ASH abstract).

27. Othus M, Appelbaum F, Petersdorf S, Erba H, Estey E. Evaluation of which patients get a second course of 3+7 on cooperative group trials for newly diagnosed acute myeloid leukemia: a report from SWOG. Blood 2013; 122: 3925 (Abstract).

28. Othus M, Sudipto M, Sekeres M, Godwin J, Anderson J, Petersdorf S et al. Prediction of complete remission on reinduction in patients with newly diagnosed acute myeloid leukemia given intensive induction regimens: a report from SWOG and Cleveland Clinic. Blood 2013; 122: 3924 (Abstract).

29. Mell LK, Jeong J-H. Pitfalls of using composite primary end points in the presence of competing risks. J Clin Oncol 2010; 28: 4297–4299.

30. Grimwade D, Freeman SD. Defining minimal residual disease in acute myeloid leukemia: which platforms are ready for ‘prime time’? Blood 2014; 124: 3345–3355.

31. Rico JM, Miller C, Griffith M, Petti A, Spencer DH, Kettar-Kulkami S et al. Association between mutation clearance after induction therapy and outcomes in acute myeloid leukemia. JAMA 2015; 314: 811–822.

32. Chen X, Xie H, Wood B, Walter R, Pagel J, Becker P et al. Relation of clinical response and minimal residual disease and their prognostic effect on outcome in acute myeloid leukemia. J Clin Oncol 2015; 33: 1258–1264.

33. Inaba H, Coustan-Smith E, Cao X, Pounds S, Shurtleff S, Wang K et al. Comparative analysis of different approaches to measure treatment response in acute myeloid leukemia. J Clin Oncol 2012; 30: 3625–3632.

34. Buccissano F, Maurillo L, Del Principe M, Del Poeta G, Sconocchia G, Lo Coco F et al. Prognostic and therapeutic implications of minimal residual disease detection in acute myeloid leukemia. Blood 2012; 119: 332–341.

35. Freeman S, Virgo P, Couzens S, Grimwade D, Russell N, Hills R et al. Prognostic relevance of treatment response measured by flow cytometric residual disease detection in older patients with acute myeloid leukemia. J Clin Oncol 2013; 31: 4123–4131.

36. Walter R, Gooley T, Wood B, Milano F, Fang F, Sorror M et al. Impact of pretransplantation minimal residual disease as detected by multiparametric flow cytometry on outcome of myeloablative hematopoietic cell transplantation for acute myeloid leukemia. J Clin Oncol 2011; 29: 1190–1197.

37. Sargent DF, Shi O, De Bono J, Cloughesy T, Fowler N, Fu T et al. Evaluation of complete response rate at 30 months as a surrogate for progression-free survival in first-line follicular lymphoma studies: results from the prospectively specified Follicular Lymphoma Analysis of Surrogacy Hypothesis (FLASH) analysis with individual patient data of 3,837 patients. J Clin Oncol 2015; 33: 8504 (abstract).

38. Gale RP. Measurable residual disease (MRD): much ado about nothing? Bone Marrow Transplant 2015; 50: 163–164.

39. Petersdorf SH, Kopecky KJ, Slovak M, Willman C, Neville T, Brandwein J et al. A phase 3 study of gemtuzumab ozogamicin during induction and postconsolidation therapy in younger patients with acute myeloid leukemia. Blood 2013; 121: 4854–4860.
42 Othus M, Wood B, Estey E, Petersdorf S, Appelbaum F, Erba H et al. Effect of minimal residual disease (MRD) information on prediction of relapse and survival in adult acute myeloid leukemia (SWOG S0106). (Submitted).

43 Mahan FX, Rea D, Guilhot J, Guilhot F, Huguet F, Nicolini F et al. Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicenter Stop Imatinib (STIM) trial. Lancet Oncol 2010; 11: 1029–1035.

44 McDermott D. Update on the application of Interleukin-2 in the treatment of renal cell carcinoma. Clin Cancer Res 2007; 13 (2 Suppl): 716s–720s.

45 Campigotto F, Weller E. Impact of informative censoring on the Kaplan-Meier estimate of progression-free survival in phase II clinical trials. J Clin Oncol 2014; 32: 3068–3074.

46 Alibhai S, Laech M, Gupta V, Tomlinson G, Brandwein J, Suarez Saiz F et al. Quality of life beyond 6 months of initial diagnosis in older adults with acute myeloid leukemia. Crit Rev Oncol Hematol 2009; 69: 168–174.