Relationship between event-free survival and overall survival in acute myeloid leukemia: a report from SWOG, HOVON/SAKK, and MRC/NCRI

Much recent attention has been given to evaluating surrogate endpoints for overall survival (OS) in various cancers. Valid surrogate endpoints for OS can reduce sample size, reduce follow-up duration, and decrease costs for trials. The US Food and Drug Administration (FDA) has approved new drugs in several cancers using progression-free survival (PFS) rather than OS as the criterion for approval.[1,2]

Nonetheless, the principal criterion used by the FDA for approval of new drugs in acute myeloid leukemia (AML) remains an improvement in OS. However, the approval of new drugs in AML might be hastened if event-free survival (EFS), an endpoint that bears resemblance to PFS, replaced OS as the basis for new drug approval in AML. Surrogate endpoints such as EFS need to be validated for each tumor type, treatment, and stage of disease; leukemia-free survival has recently been shown to be a surrogate for OS for AML patients in remission receiving IL-2 maintenance therapy.[3]

One commonly used definition of surrogacy requires two conditions to be met: 1) OS and EFS are correlated and 2) treatment effects (e.g., hazard ratios) on OS and EFS are correlated.[4] We evaluated the first condition of surrogacy in 3,877 adults with newly diagnosed AML in four separate cohorts.

The first cohort was 595 patients age <60 with *de novo* AML treated on SWOG protocol S0106 (7+3 +/- gemtuzumab ozogamicin [GO]).[5] The second cohort was 260 patients aged older than 60 given 7+3 with either 45 or 90 mg/m^2 daunorubicin on HOVON/SAKK study H043.[6] The third cohort was 133 SWOG patients given azacitidine + GO in SWOG S0703.[7] The fourth cohort was 2,889 patients from the MRC trial AML15.[8] SWOG criteria for AML were > 20% blasts in marrow or blood while MRC and HOVON/SAKK also included patients with 10-19% blasts. Institutional review boards of the participating institutions approved all protocols, and patients were treated according to the Declaration of Helsinki.

OS was measured from the date of registration to the study to the date of death from any cause, with patients last known to be alive censored at the date of last contact. EFS was measured from the date of registration to the date of the first of: completion or going off protocol induction therapy without complete remission (CR), relapse from CR, or death due to any cause. Patients last known to be alive without an event were censored at the date of last contact. In the AML15 cohort, the date that a patient finished protocol induction therapy without CR was not available. We imputed the minimum of survival time and, as a sensitivity analysis, each of the time points 8 weeks and 12 weeks after starting induction therapy. The results for 8 and 12 weeks were similar; we present the 12 week results herein.

OS and EFS were estimated using the Kaplan-Meier method. The correlation between EFS and OS was evaluated using Kendall's tau, a measure of correlation appropriate for data with censoring.[9] Perfect concordance has a correlation of 1, perfect discordance has a correlation of -1, and independent measures (no correlation) have a correlation of 0.

Within trial S0106, the correlation between EFS and OS was 0.50 (95% confidence interval [CI] 0.33- 0.66).

Table 1. Summaries of studies. N(%) and median (range) reported.

	S0106	H043	AML15	S0703
Patient N.	595	260	2889	133
Registration year	2008 (2004-2009)	2004 (2001-2006)	2006 (2002-2009)	2010 (2009-2012)
Age	47 (18-60)	67 (61-78)	50 (16-73)	73 (60-88)
Treatment	7+3±GO	7+3	10+3 +/-E +/-GO; ADE *vs.* FLAG –ida each +/- GO	Aza+GO
Deaths	302 (51%)	232 (89%)	1648 (57%)	119 (89%)
EFS events	405 (68%)	239 (92%)	(66%)	131 (98%)
No CR1	179 (30%)	75 (29%)	433 (15%)	98 (74%)
Death w/o CR1	129 (22%)	75 (29%)	426 (15%)	89 (67%)
Relapse after CR1	186 (31%)	133 (51%)	1153 (40%)	26 (20%)
Death after relapse	133 (22%)	126 (48%)	889 (31%)	23 (17%)
Death in CR1	40 (7%)	31 (12%)	333 (12%)	7 (5%)
Alive w/o CR1	50 (8%)	0	7 (<1%)	9 (7%)
Follow-up (years)	5.2 (0.4, 9.0)	–	3.3 (0.4-7.0)	2.7 (2.1-5.9)
Alive after relapse	53 (9%)	7 (3%)	264 (9%)	3 (2%)
Follow-up (years)	5.5 (3.2, 8.8)	8.5 (7.8-11.1)	4.5 (2.0-8.4)	2.8 (2.5-5.0)
Alive w/o relapse	190 (32%)	21 (8%)	970 (34%)	2 (2%)
Follow-up (years)	5.3 (0.3, 9.0)	9.3 (7.0-11.6)	4.7 (0.2-8.5)	2.4 (0.6-4.2)
Kendall's tau	0.50 (0.33, 0.66)	0.66 (0.39, 0.92)	0.11 (0, 0.32)	0.19 (0.14, 0.23)

CR1: complete remission during induction; w/o: without; GO: gemtuzumab ozogamicin; Aza: azacitidine; E: etoposide; ADE : cytarabine + daunorubicin + etoposide; FLAG-ida: fludarabine + cytarabine + idarubicin + G-CSF during chemotherapy.

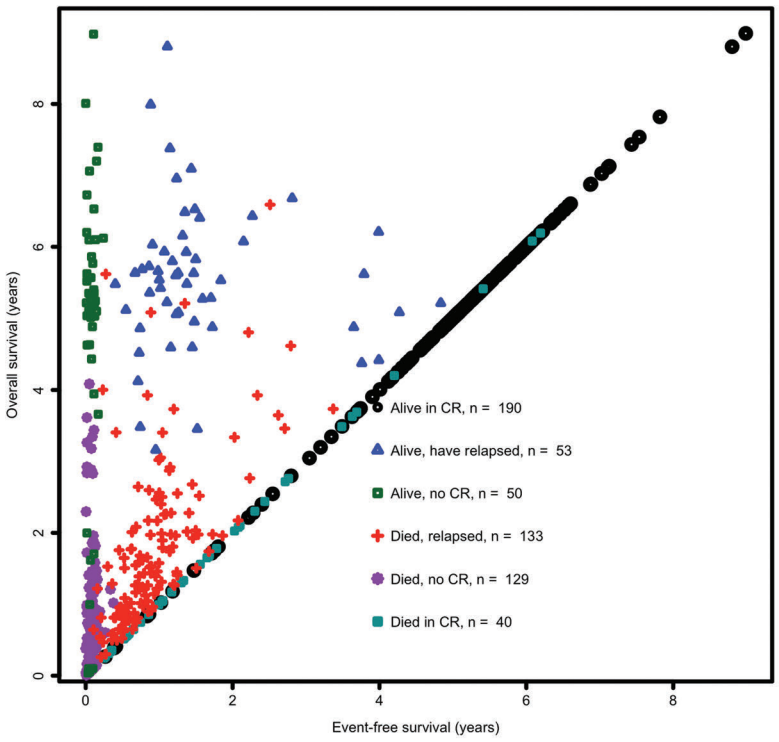

Figure 1. Scatterplot of EFS and OS for the S0106 cohort.

Within H043, the correlation was 0.66 (95% CI 0.39-0.92). For S0703, the correlation was 0.11 (95% CI 0-0.32). For AML15 the correlation was 0.19 (95% CI 0.14-0.23). The CI for S0703 includes 0 consistent with no correlation. For S0106, H043, and AML15, the CI excludes 0, indicating a significant positive correlation.

Though the correlations between EFS and OS for S0106, H043, and AML15 were significantly greater than 0, the magnitude of the correlation was still modest. Figure 1, based on the S0106 data, illustrates why this is the case. Each patient is represented by a symbol. Patients on the 45-degree line are currently alive in CR or died in CR and thus have EFS equal to OS. All other patients have longer OS than EFS. By definition, a patient cannot have longer EFS than OS. A large number of patients never achieved a CR on S0106, then received salvage therapy and had long OS but very short EFS, since failure to attain CR is an event in the definition of EFS (green squares in Figure 1). Also, there are a number of patients who relapsed from their initial CR but received salvage therapy and have long OS (blue triangles and some red crosses in Figure 1).

The slightly higher correlation estimate in H043 than S0106 could reflect the better protocol adherence in the former, with some S0106 patients who might have achieved CR with a second protocol course not receiving it, and instead receiving an alternative non-protocol therapy. The reason for the much poorer correlation between EFS and OS in S0703 and AML15 compared to the other two studies is not clear. For AML15, many patients relapsed (779), but there were also a large number of patients with long OS after their relapse. Among the 192 patients still alive after relapse, the median survival time was 2.6 years. This may have reflected the successful use of allogeneic hematopoietic cell transplant (HCT) after relapse in a substantial number of patients.[10] For S0703, one possibility is that the CRs were of particularly poor quality because of persistent minimal residual disease (MRD) due to the less intensive regimen, thus predisposing patients to rapid relapse. Arguing against this possibility, the median time to relapse did not appear grossly different in any of the studies (10 months in S0106, 9 months in H043, 7 months in S0703, and 12 months in AML15). Certainly it has been questioned whether with azacitidine therapy a CR is required to improve OS, or whether disease "stabilization" is enough, and azacitidine was used with GO in S0703.

The correlation between EFS and OS in the HOVON/SAKK data set is similar to that reported between an elevated prostate-specific antigen test and a biopsy-proven diagnosis of prostate cancer,[11] or between the HCT comorbidity index (HCT-CI) and death after HCT.[12] Nonetheless, we found it difficult to conclude that EFS would be a strong surrogate for OS in newly diagnosed AML. A similar conclusion might be reached from a Kendall's tau value of 0.47 (95% CI 0.43, 0.51) found by ECOG for the correlation of EFS/OS in the E1900 trial.[13] We did not evaluate the second criterion for the definition of surrogacy as previously described, because we felt the first criterion was not met, and both criteria are required to be met for a true surrogate. The relation between EFS and OS in relapsed or refractory AML remains unexplored, as does that between relapse-free survival (RFS, relapse and death as events) and OS in patients who receive HCT, although a correlation between RFS and OS was reported in a trial administering IL-2 + histamine to patients in remission.[3]

Analyzing RFS instead of EFS in the cohorts herein would increase Kendall's tau by excluding patients who failed to achieve CR, thereby decreasing the number of patients with widely disparate EFS and OS measurements. For example, in S0106 Kendall's tau for RFS and OS after CR was 0.65. We focused our analysis on EFS because, similar to OS, it is defined for all patients, not

just the subset of patients who achieve a CR. As long as patients who do not achieve a CR or relapse can be salvaged (including by HCT)[14] or live long enough to receive several salvage therapies, the correlation between EFS and OS in AML will remain modest.

The use of CR without minimal residual disease (MRD) as identified by multi-parameter flow cytometry, or the persistence of molecular genetic abnormalities may be better able to identify long-term survivors than conventional CR, used herein. However, considering CR accompanied by MRD as an event would decrease EFS compared to the criteria we used, which do not distinguish between CR +/- MRD. Because OS would not change, the correlation between EFS and OS would also decrease.

Nonetheless, several reasons lead us to believe that EFS may have value as an alternative endpoint for OS. First is the possibility that remission, and in particular CR, has real clinical value. Patients in remission for some time very plausibly have a better quality of life (QOL) consequent to a reduced frequency of transfusions, less time spent in hospital for treatment of infections, and a more hopeful view of their future. Studies in melanoma have demonstrated improved QOL while patients are disease-free.[1] The FDA's approval of new drugs for colorectal cancer[2] and adjuvant treatment of melanoma,[1] despite a failure to improve OS, might serve as precedents for a similar approach in AML. In addition, unlike OS, EFS is not influenced by therapy given after failure to attain, or relapse from, remission, and so may provide a more direct assessment of the benefit of a therapy given during induction. Notably several drugs, including clofarabine,[15] and sorafenib,[15] have lengthened EFS but not OS in AML. The use of EFS as a basis for new drug approval in AML could lead to more therapeutic options for AML patients.

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