Leukemia-free survival as a surrogate end point for overall survival in the evaluation of maintenance therapy for patients with acute myeloid leukemia in complete remission

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ABSTRACT

Background
In trials designed to evaluate new therapies for hematologic malignancies, end points such as leukemia-free survival are often used as surrogates for overall survival in acute leukemia. We aimed to assess whether leukemia-free survival is an acceptable statistical surrogate for overall survival when applied to remission maintenance therapy for acute myeloid leukemia.

Design and Methods
Data were analyzed from a randomized Phase III trial of remission maintenance immunotherapy with histamine dihydrochloride plus low-dose interleukin-2 *versus* no treatment in adults with acute myeloid leukemia. A two-stage surrogate validation model was applied in which correlations between Kaplan-Meier estimates of leukemia-free survival and overall survival, and between log hazard ratios reflecting treatment effects were analyzed. Country of patient enrollment was the unit of analysis.

Results
Kaplan-Meier estimates of overall survival at 36, 48, and 60 months and leukemia-free survival at 24 months were reasonably correlated (R^2 ranging from 0.44 to 0.84) both for the overall (n=320) and first complete remission (n=261) populations. The effects of histamine dihydrochloride/interleukin-2 on log hazard ratios for leukemia-free survival and overall survival were well correlated (R^2=0.88-0.93).

Conclusions
The significant correlations between overall survival and the surrogate end point (leukemia-free survival) and between the effect of histamine dihydrochloride/interleukin-2 on leukemia-free survival and overall survival satisfy the two-stage surrogate validation model. *(ClinicalTrials.gov Identifier: NCT00003991)*

Key words: leukemia-free survival, overall survival, immunotherapy, statistical analyses, clinical trial interpretation.

Citation: Buyse M, Michiels S, Squifflet P, Lucchesi KJ, Hellstrand K, Brune ML, Castaigne S, and Rowe JM. Leukemia-free survival as a surrogate end point for overall survival in the evaluation of maintenance therapy for patients with acute myeloid leukemia in complete remission. Haematologica 2011;96(8):1106-1112. doi:10.3324/haematol.2010.039131

Acknowledgments: the authors are grateful to Dr S. George and two anonymous referees for their useful comments, and to Donald Fallon, MA, ELS, of MedVal Scientific Information Services, LLC for editorial assistance. This work was presented at the 13th Congress of the European Hematology Association, June 12-15, 2008, Copenhagen, Denmark. Haematologica. 2008;93 (Suppl 1):209-10. Abstract 519.

Funding: funding to support these analyses and preparation of this paper was provided by EpiCept Corporation. EpiCept Corporation did not contribute to any of the analyses presented here, nor to their interpretation.

Manuscript received on December 13, 2010. Revised version arrived on April 11, 2011. Manuscript accepted on April 12, 2011.

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Introduction

Increasing attention is being focused on the use of alternative end points to overall survival (OS) in cancer therapy clinical trials.[1] The large sample sizes, long follow-up durations, and considerable costs and effort invested in completing clinical trials could be substantially reduced if valid alternative or surrogate end points to overall survival were identified.[2]

Progression-free survival and disease-free survival in advanced and early-stage colorectal cancer, respectively, are among the best studied, validated, and generally accepted surrogate end points for overall survival.[3-6] Other time-to-event end points such as time-to-progression or time-to-disease recurrence have been proposed to substitute for overall survival in treatment trials of other solid tumors, including trials investigating breast,[7-9] prostate,[10] ovarian,[11] glioblastoma,[12] non–small cell lung,[13,14] head and neck,[15] gastric,[16] and pancreatic[17] cancers. In many circumstances, such end points are in fact more reliable and sensitive indicators of treatment efficacy than overall survival because more events are observed for these end points than for overall survival and they are not confounded by post-progression therapies.[2,18,19]

Although progression-free survival is often an acceptable surrogate for overall survival, in the case of breast cancer, for example, the potential of progression-free survival to predict overall survival is uncertain.[7-9] Therefore, ideally the validity of a particular surrogate needs to be verified by tumor type, treatment, and stage of disease for which the treatment is intended.

In hematologic malignancies, end points such as hematologic response, molecular response, or time-to-disease relapse are often used as end points of clinical trials. In acute myeloid leukemia (AML), for example, leukemia-free survival (LFS) is undoubtedly a clinically relevant end point because relapse in AML signifies a reduced quality of life and substantial morbidity or mortality resulting either from the use of toxic salvage therapies, disease progression, or both.[20-22] For patients with AML who achieve complete remission (CR) after induction and consolidation therapy, delaying or preventing relapse is critical to long-term survival or cure.[21] Yet in spite of the clear clinical relevance of prolonging time to disease recurrence, regulatory agencies typically approve new treatments that are reasonably likely to prolong survival and/or improve quality of life, since these are the two principal goals of all cancer therapies.[3,23] It is, therefore, important to be able to distinguish between a treatment that significantly prolongs leukemia-free survival with no impact whatsoever on overall survival (perhaps as a result of some unfavorable effect of treatment on other causes of mortality), and one that significantly prolongs leukemia-free survival but fails to achieve statistical significance on overall survival (perhaps because of a lack of statistical power). The acceptability of leukemia-free survival as a potential surrogate end point for overall survival is particularly relevant in the setting of maintenance therapy for AML because interpretation of overall survival data after long follow-up periods can easily be confounded by intercurrent events, including deaths unrelated to leukemia, or by variable effects of post-relapse therapies on survival.[24]

To evaluate the utility of leukemia-free survival as a surrogate end point for overall survival, results were analyzed from a randomized phase III trial of histamine dihydrochloride (HDC) plus low-dose interleukin-2 (IL-2) in AML patients in remission. The trial achieved its primary end point, in that treatment with HDC/IL-2 for up to 18 months significantly prolonged leukemia-free survival in AML patients compared to untreated patients,[25] although results of overall survival did not achieve statistical significance.

Design and Methods

Phase III trial of HDC/IL-2 as remission maintenance therapy for AML patients in CR

This was a randomized, multinational, open-label phase III trial (NCT00003991) of AML patients (n=320) who had achieved complete remission after induction and consolidation treatment according to usual practice at each investigative center (n=100). The trial was conducted according to the ethical principles stated in the Declaration of Helsinki (October 1996). The protocol, amendments, and sample informed consent forms were reviewed and approved at each of 92 distinct clinical centers by a duly constituted Institutional Review Board or Independent Ethics Committee. The largest subset of patients were in first remission (CR1; n=261). Safety and efficacy of immunotherapy with HDC (Ceplene®, EpiCept Corporation, Tarrytown, NY, USA) given subcutaneously (sc) at a dose of 0.5 mg twice daily (bid) in conjunction with low-dose IL-2 (Proleukin®, Chiron, Emeryville, CA [now Prometheus® Therapeutics and Diagnostics, San Diego, CA, USA]) at 1 μg/kg (16,400 IU/kg) sc bid was compared to the standard-of-care. Following initial supervision and training to perform sc injections, treatments were self-administered by patients for up to ten 3-week cycles over a period of up to 18 months. Control (standard-of-care) patients received no treatment during this period.

The primary objective of the trial was to determine if HDC/IL-2 could prolong duration of leukemia-free survival compared to no treatment. Leukemia-free survival was defined as the time from the date of randomization to the date of relapse of AML or death from any cause, whichever came first. As used in this analysis, leukemia-free survival was determined by the absence of peripheral blood evidence or clinical evidence of relapse. The effect of HDC/IL-2 on overall survival was a secondary end point.

Treatment with HDC/IL-2 was well tolerated, with no treatment-related mortality, no significant morbidity, nor any detrimental impact on quality of life.[26] Details regarding trial design and conduct, patients' characteristics, and results, including assessments of HDC/IL-2 maintenance therapy on patients' quality of life, have been previously reported.[25,26] Briefly, the HDC/IL-2 treated and untreated groups were balanced across all demographic and disease prognostic variables, both in the overall and CR1 populations. All efficacy analyses were performed as intent-to-treat (ITT). After a median follow up of 48 months, a statistically significant benefit of HDC/IL-2 was demonstrated for the primary leukemia-free survival end point for all patients (n=320; hazard ratio [HR]=1.43; 95% CI=1.10, 1.87) and for patients in CR1 (n=261; HR=1.46; 95% CI=1.09, 1.97) (P=0.008 and P=0.012; log rank test stratified by country and complete remission status, respectively). The HR reflecting between-group differences in overall survival for the overall population was 1.23 (95% CI=0.92, 1.65; P=0.16), and for patients in CR1 was 1.30 (95% CI=0.94, 1.80; P=0.12).

Determining the utility of LFS as a surrogate for OS

For leukemia-free survival to be considered a valid surrogate for overall survival with respect to a treatment (in this case, HDC/IL-2), two conditions must hold (Figure 1).[23] Condition #1 requires that both end points (OS and LFS) be correlated. Condition #2 requires that the treatment effects measured on both end points also be correlated. The strength of the correlations reflects the quality of the surrogate, that is, perfect surrogates would be expected to yield correlation coefficients equal to 1.

Countries rather than individual clinical sites were chosen as the unit of analysis because most sites enrolled too few patients to be considered individually in the analyses. Patients enrolled in the trial in the same country were grouped together, with the understanding that multiple sites may have contributed patients in each country.

Condition #1 was tested by performing weighted linear regression analyses (WLRA) between country-specific Kaplan-Meier estimates of overall survival at 36, 48, and 60 months *versus* Kaplan-Meier estimates of leukemia-free survival at 24 months. Data for each country were weighted by the effective sample size at the time point considered for Kaplan-Meier estimates (number of deaths prior to the time point plus the number of patients at risk at the time point). The association between leukemia-free survival and overall survival was also explored through a bivariate copula model fitted on individual patient data. Kendall's τ was used to quantify the correlation between the end points.[4] This model is more satisfactory in that the correlations reflect the whole time axis instead of Kaplan-Meier estimates at specific time points.

Condition #2 was tested by fitting a linear regression model on treatment effects on leukemia-free survival and overall survival. The coefficient of determination (R^2) was used to quantify the proportion of variance explained by the regressions. All analyses were performed for the overall and CR1 populations treated as separate datasets. All R^2 and Kendall's τ reported differed significantly from 0 ($P<0.05$).

Model accuracy

To assess model accuracy, we applied a "leave-one-out" cross-validation strategy as follows: each country was left out once and the weighted linear model was then constructed using the other countries.[23] This model was then re-applied to the country that had been left out in order to compare the predicted and observed treatment effect on overall survival. Based on the weighted linear regression models, 95% prediction intervals were calculated for a country equal in size to that of the country left out.

Results

The country-specific Kaplan-Meier estimates of overall survival at 36 months *versus* leukemia-free survival at 24 months for the overall and CR1 populations are shown in Figure 2. For the overall population (Figure 2A), the WLRA equation was $OS_{36}=0.24 + 0.64 \times LFS_{24}$ with a coefficient of determination, $R^2=0.63$, indicating that about two-thirds of the variance could be explained by the linear regression. Similarly, for the CR1 population (Figure 2B), the WLRA equation was $OS_{36}=0.22 + 0.74 \times LFS_{24}$, and $R^2=0.61$. Country-specific Kaplan-Meier estimates of overall survival at 36 months were correlated with the Kaplan-Meier estimates of leukemia-free survival at 24 months, suggesting that Condition #1 of the surrogacy model was reasonably satisfied. Further exploration of Condition #1 of the surrogacy model using different follow-up durations for overall survival also showed reasonable correlations between the country-specific Kaplan-Meier estimates of 48- and 60-month overall survival with 24-month leukemia-free survival for the overall population (Table 1). A bivariate copula model revealed that overall survival and

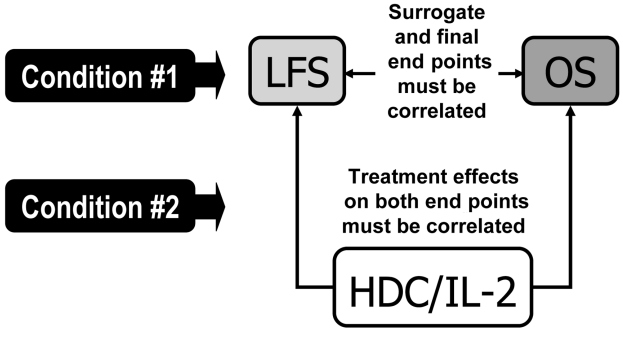

Figure 1. Two-stage validation model for LFS as a surrogate for OS in a trial of HDC/IL-2 as remission maintenance therapy in AML.

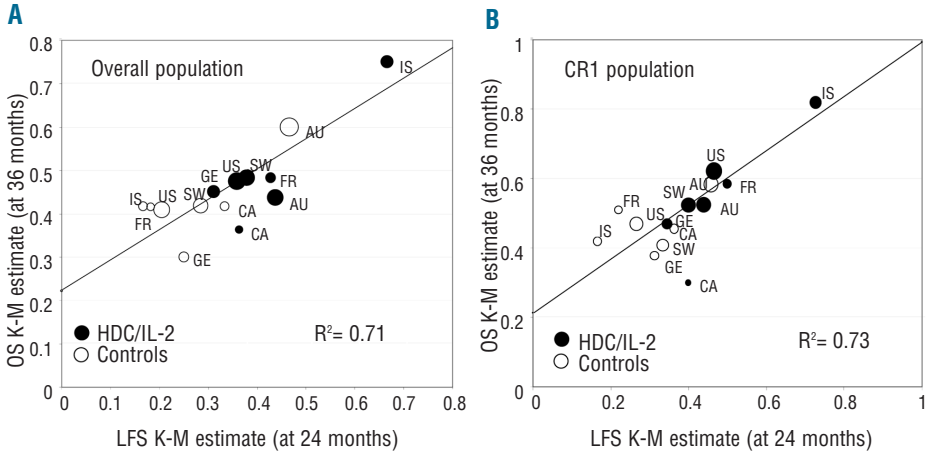

Figure 2. Kaplan-Meier (K-M) estimates of OS at 36 months *versus* LFS at 24 months for HDC/IL-2-treated AML patients and controls. Weighted linear regression analyses (WLRA) were performed to test Condition #1 in the surrogate validation model (see main text and Figure 1). The WLRA reflect the overall (A) and CR1 (B) populations grouped by treatment and country. Circle size is proportional to the number of patients in each country. US=United States; AU=Australia (including New Zealand); SW=Sweden; GE=Germany; FR=France; IS=Israel; CA=Canada. The WLRA equations (see main text) revealed good correlations between OS and LFS for both the overall and CR1 populations, satisfying Condition #1 of the model.

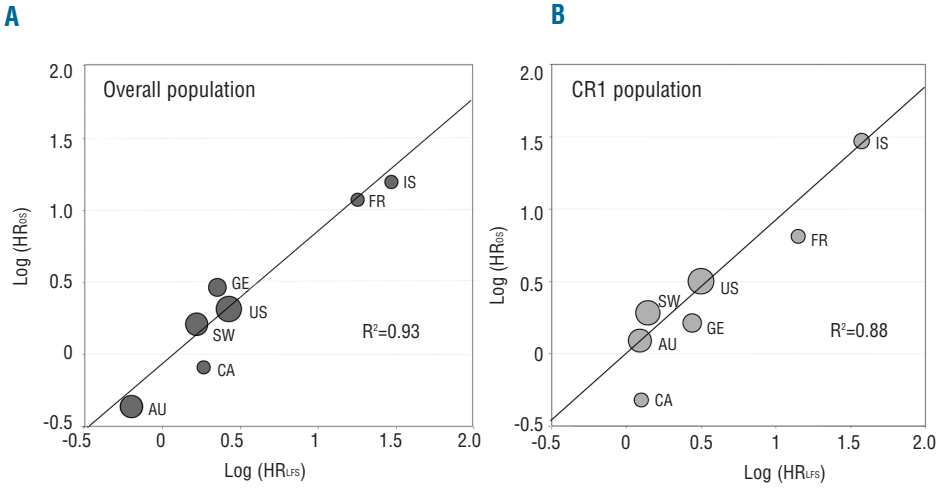

Figure 3. Logarithms of OS hazard ratios *versus* logarithms of LFS hazard ratios for patients grouped by country. Weighted linear regression analyses (WLRA) were performed to test Condition #2 in the surrogate validation model (see main text and Figure 1). The WLRA reflect the overall (A) and CR1 (B) populations grouped by treatment and country. Circle size is proportional to the number of patients in each country. US = United States; AU = Australia (including New Zealand); SW = Sweden; GE = Germany; FR = France; IS = Israel; CA = Canada. The WLRA equations (see main text) revealed good correlations between the OS and LFS hazard ratios for both the overall and CR1 populations, satisfying Condition #2 of the model.

Table 1. Linear regressions correlating country-specific Kaplan-Meier estimates of LFS at 24 months and OS at 36, 48, and 60 months.

All patients Weighted Linear Regression Equation	R^2	CR1 patients Weighted Linear Regression Equation	R^2
$OS_{36} = 0.24 + 0.64 \times LFS_{24}$	0.64	$OS_{36} = 0.22 + 0.74 \times LFS_{24}$	0.61
$OS_{48} = 0.13 + 0.69 \times LFS_{24}$	0.44	$OS_{48} = 0.08 + 0.83 \times LFS_{24}$	0.45
$OS_{60} = 0.06 + 0.84 \times LFS_{24}$	0.84	$OS_{60} = 0.01 + 0.94 \times LFS_{24}$	0.64

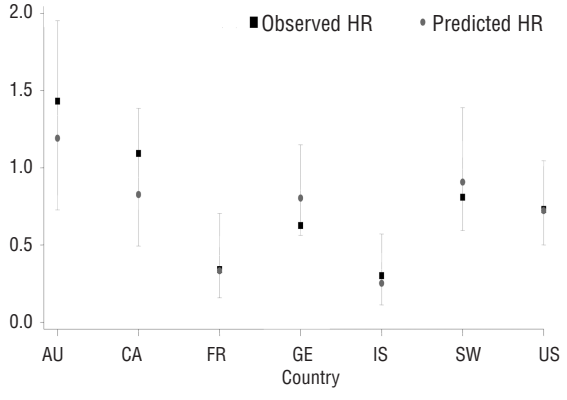

Figure 4. "Leave-one-out" cross-validation analysis. Gray circles correspond to the predicted country-specific hazard ratios for overall survival using the observed country-specific hazard ratios for leukemia-free survival and the surrogate model built on all other countries, gray vertical lines to 95% prediction intervals and black squares to the observed country-specific hazard ratios for overall survival. US=United States; AU=Australia (including New Zealand); SW=Sweden; GE=Germany; FR=France; IS=Israel; CA=Canada.

leukemia-free survival were also correlated at the level of the individual patient: Kendall's τ=0.68 with a 95% CI (0.63-0.72). For the CR1 population, Kendall's τ=0.70 with a 95% CI (0.65-0.75).

Condition #2 of the surrogate validation model requires that the treatment effect on the traditional end point (OS) and the proposed surrogate (LFS) be correlated. By our analyses, the country-specific log HRs reflecting the treatment effect of HDC/IL-2 on overall survival and leukemia-free survival were highly correlated (Figure 3). The WLRA equation for the overall population (Figure 3A) was $\log(HR)_{OS} = -0.08 + 0.93 \times \log(HR_{LFS})$ with a coefficient of determination $R^2=0.93$, indicating that 93% of the variance could be explained by the linear regression. The observed effect of treatment on leukemia-free survival was a good predictor of the treatment effect on overall survival, with only a slight (7%) attenuation of the effect as reflected in the slope of 0.93. Additionally, the fitted regression line nearly passed through the origin, indicating that no effect on leukemia-free survival predicts that there would be no effect on the overall survival end point, a condition expected of a good surrogate. Similarly, for the CR1 population (Figure 3B), the WLRA equation was $\log(HR)_{OS} = -0.02 + 0.88 \times \log(HR_{LFS})$ with $R^2=0.88$. With Condition #2 thus fulfilled, the effect of treatment with HDC/IL-2 on leukemia-free survival would be expected to predict the effect of treatment on overall survival for the overall and CR1 populations.

The predicted results from the cross-validation analysis are shown in Figure 4. The observed hazard ratios fell within the 95% prediction intervals in all countries. Almost no variation in the coefficient of determination was observed during the cross-validation, with values ranging from $R^2=0.89$ to $R^2=0.96$.

Discussion

The issue of surrogacy of time-to-event end points such as progression-free survival, disease-free survival, and leukemia-free survival in oncology clinical trials has generated much debate in the last decade.[1,27] Substitution of a surrogate end point for overall survival has practical,[28] clinical,[29] and regulatory[30] implications, emphasizing the importance of demonstrating that the surrogate reliably reflects the traditional end point.[18] The appropriateness of progression-free survival and disease-free survival as sur-

rogate end points has been well established in early- and advanced-stage colorectal cancer.[3-6] However, the predictive power of a particular surrogate for overall survival is not equivalent for all diseases (e.g. strong in the case of colorectal cancer but weak in the case of advanced breast cancer),[7-9] and the use of surrogate end points is not automatically acceptable in all tumor types or stages of disease. For example, in validation analyses of surrogate end points in metastatic breast cancer studies,[7,8] the rank coefficient between treatment effects on progression-free survival and overall survival of 0.48 (95% CI: –0.34 to 1.30) was too imprecise to accept progression-free survival as a surrogate for overall survival. For this reason, surrogate end points need to be examined and validated by tumor type and treatment, and possibly for the stage of disease for which the treatment is intended.

In this trial of remission maintenance therapy with HDC/IL-2, the Kaplan-Meier estimates of overall survival at 36 months and Kaplan-Meier estimates of leukemia-free survival at 24 months were well correlated for both the overall and CR1 populations. When evaluated at the level of the individual patient and for longer follow-up durations (OS at 48 and 60 months), the correlations remained robust. More importantly, strong correlations between treatment effects of leukemia-free survival and overall survival were observed, indicating that the HDC/IL-2 treatment effect on leukemia-free survival is a good predictor of the treatment effect on overall survival. Although the question as to what is a large enough correlation is to some extent subjective, it is reasonable to claim that the two conditions schematized in Figure 1 are satisfied, and hence leukemia-free survival meets the criteria as a valid surrogate for overall survival. Other criteria have been proposed in the literature for the validation of surrogate end points, but those adopted here have been used extensively in solid tumors both in the adjuvant treatment and advanced disease settings.[3-5,7,13,15,16,23,31-34]

The trial on which this analysis was based did not achieve significance in its secondary overall survival end point; however, it is noteworthy that the presence or lack of a significant overall survival benefit appears to have little bearing on the success or failure of surrogate validations in solid tumor trials.[3,7] With the available follow-up data in the HDC/IL-2 trial at the time of the database lock, 236 patients had experienced an event contributing to the leukemia-free survival end point (110 in the treatment group and 126 in the control group). Contributing to the overall survival end point, 196 patients had died (94 in the treatment group and 102 in the control group). Hence, the power of the leukemia-free survival analysis was higher than that of the overall survival analysis for the same postulated treatment effect.

Statistically significant overall survival end points in cancer trials are difficult to achieve. Examples of non-significant overall survival results are plentiful despite significant and clinically meaningful progression-free survival or disease-free survival outcomes.[35-38] As noted by Yothers,[18] overall survival is a composite end point, based on death caused by: i) the original cancer; ii) treatment; iii) another cancer; or iv) other causes. Of these, only the first two factors directly measure the treatment effect, and the other factors could be confounding. Disease-free survival (or progression-free survival) is also a composite, as this end point takes into account all of the above plus the following additional factors: v) malignant expansion; and vi) development of a second cancer of the same histological type. Because more of the factors contributing to the measurement are relevant, confounding factors (i.e. other causes) are minimized and end points such as disease-free survival (or progression-free survival) are more sensitive to the true treatment effect.[18] In fact, time to relapse or disease progression (with censoring of non-malignant deaths occurring before relapse or progression) would be even more sensitive to treatment benefits but might miss untoward effects of therapy, and as such are less desirable to assess the overall impact of therapy.

In trials evaluating therapies in AML, many factors can impact on the detection of a statistically significant overall survival benefit. Firstly, AML is a relatively rare disease and enrollment of patients in large enough numbers to adequately power a study for overall survival is a major challenge. Secondly, long follow-up durations are required, during which practice patterns change and affect overall survival in ways extraneous to the treatment effect. Thirdly, most AML patients are older and have a higher probability of death than younger patients (5-year survival rates are 4% in patients 65 years of age and over, and 31% in patients under 65 years of age, respectively).[39] Applying the principles set forth by Yothers,[18] deaths unrelated to leukemia in older patients can potentially confound interpretation of overall survival data. Finally, and with particular relevance to the study of remission maintenance therapies in AML, such patients may receive salvage therapies post relapse. Post-relapse salvage therapies are far from standardized and may have different mortality risks, and thus any observed differences in overall survival might result from such therapies rather than from the randomized intervention.

For these reasons, leukemia-free survival may be more appropriate than overall survival to assess the benefit of strategies to prevent AML relapse. Other AML trials conducted by major cooperative groups (e.g. NHLBI, CALGB, ECOG, NCI, SWOG, and EORTC) often use leukemia-free survival as the primary end point. As is typical in this and other studies of remission maintenance, leukemia-free survival is determined by the absence of evidence of relapse in peripheral blood or clinical symptoms. Periodic bone marrow sampling to confirm relapse would no doubt improve the robustness of leukemia-free survival as an end point, but routine bone marrow examination over the long term is a burden on patients and may not be feasible. Validation of leukemia-free survival as a surrogate end point will increase the acceptability of results from such trials and help to streamline future clinical trial design. The present analyses are the first to critically examine this concept in a therapeutic trial for AML and provide evidence that leukemia-free survival is an acceptable surrogate for overall survival. The relationship identified here between treatment effects on leukemia-free survival and overall survival may also be useful to guide future trial designs, insofar as they suggest that treatment effects on overall survival will be systematically lower than treatment effects on leukemia-free survival by approximately 10% (the log(HR) for overall survival was lower than the log(HR) for leukemia-free survival by 7% for all patients and by 12% for CR1 patients).

Since the available data were from a single trial, we grouped patients by country and performed the validation using countries as units of analysis. Whereas a meta-analysis of several trials might have yielded more convincing

evidence than a single trial, other surrogate end points have been validated using centers or countries as the units of analysis when the number of trials was limited.[32-34] The cross-validation performed using a "leave-one-out" approach provides some reassurance that the results were robust.[15] Even so, our results should be confirmed in an independent trial or set of trials.

To conclude, the two conditions for surrogacy of leukemia-free survival for overall survival were reasonably satisfied in these analyses. Pending confirmation in an independent dataset, these results support the use of leukemia-free survival as the primary end point for future AML trials of remission maintenance therapies.

Authorship and Disclosures

The information provided by the authors about contributions from persons listed as authors and in acknowledgments is available with the full text of this paper at www.haematologica.org.

Financial and other disclosures provided by the authors using the ICMJE (www.icmje.org) Uniform Format for Disclosure of Competing Interests are also available at www.haematologica.org.

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