

**Individual patient data meta-analysis of randomized trials evaluating interleukin-2 monotherapy
as remission maintenance therapy in acute myeloid leukemia**

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ABSTRACT

Interleukin-2 (IL-2) is a natural T-cell derived cytokine that stimulates the cytotoxic functions of T and natural killer cells. IL-2 monotherapy has been evaluated in several randomized clinical trials (RCTs) for remission maintenance in patients with acute myeloid leukemia (AML) in first complete remission (CR1); none demonstrated a significant benefit of IL-2 monotherapy. The objective of this meta-analysis was to reliably determine IL-2 efficacy by combining all available individual patient data (IPD) from 5 RCTs (n=905) and summary data from a 6th RCT (n=550). Hazard ratios (HRs) were estimated using Cox regression models stratified by trial, with $HR < 1$ indicating treatment benefit. Combined IPD showed no benefit of IL-2 over no treatment in terms of leukemia-free survival, LFS ($HR=0.97$; $P=0.74$) or overall survival, OS ($HR=1.08$; $P=0.39$). Analyses including the 6th RCT yielded qualitatively identical results (LFS $HR=0.96$, $P=0.52$; OS $HR=1.06$; $P=0.46$). No significant heterogeneity was found between the trials. Prespecified subset analyses showed no interaction between the lack of IL-2 effect and any factor, including age, gender, baseline performance status, karyotype, AML subtype, and time from achievement of CR1 to initiation of maintenance therapy. We conclude that IL-2 alone is not an effective remission maintenance therapy for AML patients in CR1.

Keywords: Immunotherapy, complete remission, leukemia-free survival, overall survival, meta-analysis

INTRODUCTION

Patients with acute myeloid leukemia (AML) who achieve complete remission (CR) and subsequently relapse have very poor prospects for survival¹ and effective therapies have long been sought to maintain patients in first remission (CR1) and prevent relapse.^{2,3} One of the only interventions known to improve relapse rates in patients with AML is allogeneic hematopoietic stem cell transplantation (allo-HCT), when used as consolidation or intensification therapy. By contrast, maintenance regimens used post-consolidation aimed at preventing relapse have not been widely used in AML. Allo-SCT acts via a mechanism involving T- and natural killer (NK)-cell-mediated destruction of the leukemic clone.^{4,5,6} Interleukin-2 (IL-2) is a potent immunoactivating cytokine that stimulates tumor-specific cytotoxic T lymphocytes and NK cells.⁷ Given that strong preclinical evidence suggests a cellular pathway for the antileukemic effects of IL-2,⁸⁻¹¹ a logical question is whether IL-2, by virtue of its activity on T and NK cells, offers a pharmacotherapeutic approach to preventing relapse in AML. Clinical trials examining this therapeutic potential of IL-2 were initiated shortly after recombinant human IL-2 was introduced.^{12,13}

Initially, nonrandomized trials of IL-2 in high doses (12-24 MIU/m²/day) were reported to induce objective remissions in some patients with advanced leukemias.^{14,15} However, because toxicities of high-dose IL-2 were frequently severe or life-threatening, clinical development of IL-2 for AML was redirected to patients in CR with the goal of preventing relapse, based on the premise that these patients might benefit from IL-2 immunotherapy given at lower doses for longer periods as maintenance therapy. Patients with AML in remission were enrolled in several small nonrandomized trials of IL-2 (n = 9 to 39), the results of which, at best, suggested a modest benefit compared to historical controls.^{12,13,16-18} Results of another randomized trial comparing a higher (9 MIU/m²) to a lower (0.9 MIU/m²) dose of post-consolidation IL-2 monotherapy in AML patients showed no difference between doses and were consistent with other trials that demonstrated only a minimal benefit.¹⁹

Several randomized clinical trials (RCTs) of IL-2 monotherapy followed, each comparing the effect of a different dose of IL-2 to no treatment (ie, the standard-of-care [SOC]) on leukemia-free survival (LFS) and overall survival (OS) outcomes in AML patients in CR1.²⁰⁻²⁵ None of these RCTs found a

benefit of IL-2 monotherapy as remission maintenance in AML patients, in contrast to a small RCT in relapsed AML patients, which had shown a trend toward clinical benefit in favor of IL-2.²⁶ Taken individually, the trials of maintenance therapy only had a modest statistical power to detect small, yet potentially worthwhile, benefits of IL-2. The goal of the present meta-analysis was to achieve a higher statistical power to answer the question as to whether IL-2 alone can be considered an effective remission maintenance therapy in this population. Individual patient data were collected from all available RCTs with IL-2 monotherapy in AML patients in CR1. Subgroup analyses were performed to investigate the benefit, if any, of IL-2 in subsets of patients with different baseline prognostic factors.

MATERIALS AND METHODS

Objectives

The primary objective was to assess the efficacy of IL-2 monotherapy compared to no treatment in patients with AML who had achieved CR1. Efficacy was evaluated in terms of LFS by performing a meta-analysis on updated individual patient data (IPD) from completed RCTs of IL-2 monotherapy as remission maintenance. Secondary objectives were to assess the efficacy of IL-2 compared to no treatment in AML patients in CR1 in terms of OS and to investigate the benefit of IL-2 alone in different subgroups differentiated by age, gender, performance status, karyotype, cytological AML subtype, and time elapsed between achievement of CR1 and initiation of remission maintenance therapy. Data on induction therapy were not available for all trials and showed too much heterogeneity for reliable analysis.

Trial search and selection strategy

Trials were identified by searching the following electronic databases for Phase 2 or 3 trials of IL-2 as remission maintenance therapy in patients with AML in CR1: PubMed (Medline), Medscape, Google Scholar, Cochrane Library and Register of Clinical Trials, ClinicalTrials.gov, and conference proceedings of main congresses in hematology-oncology. In addition, investigators treating AML were contacted to

confirm the status of trials. Only RCTs conducted in patients with AML in CR1 with at least 2 study arms consisting of IL-2 monotherapy versus no treatment were included. The RCTs had to be closed to accrual and have a median follow-up of ≥ 3 years.

Fourteen trials of IL-2 in patients with AML in CR1 were identified, of which 6 met the criteria for inclusion (**Table 1**).²⁰⁻²⁵ The 8 other trials identified were excluded for the following reasons: 5 were nonrandomized^{12,13,16-18}; one was an ongoing RCT in children (age <18 years) that was still recruiting patients (NCT00149162); one was a RCT comparing two doses of IL-2 with no control (SOC) arm¹⁹; and one was a RCT of histamine dihydrochloride (HDC) in conjunction with low-dose IL-2 versus SOC (no treatment).²⁷

Data collection

The principal investigators of all eligible RCTs were asked to participate and requested to provide the most current IPD relating to remission maintenance with IL-2 versus no treatment. Specific data items utilized for the analysis included: trial, institution and patient identifiers; randomization date; treatment assigned by randomization; demographic data at baseline (date of birth or age, gender, weight, body-mass index [BMI], Eastern Cooperative Oncology Group [ECOG] performance status); karyotype (favorable, intermediate, unfavorable as defined in each trial)^{20-24,28}; cytological AML subtype; months elapsed from achievement of complete remission; treatment dose and duration (first dose, last dose, premature treatment discontinuation); reason for treatment discontinuation (disease progression, adverse event including toxic death, other reason, unknown); date of last observation (or date of death if patient died); last observation censoring indicator (alive, death); cause of death (alive, nondisease/nontoxicity, disease-related/nontoxicity, toxicity-related, unknown); date of progression (or date of last observation if patient did not progress); progression indicator (no progression, progression).

Datasets containing IPD were obtained for 5 RCTs (Blaise et al,²⁰ ALFA 9801,²¹ CALGB 9720,²² CALGB 19808,²³ and CCG 2961²⁴) for which the sample sizes, age group, IL-2 doses, and study results are summarized in **Table 1**. To facilitate comparison across the different RCTs, the average planned monthly

IL-2 doses in millions of international units (MIU) of IL-2 per m² of body surface area were derived from individual published RCTs. For one RCT (EORTC-GIMEMA 06991²⁵), results have not yet been published in full, and IPD could not yet be made available; however, the published abstract for this trial reported the LFS and OS hazard ratios (HRs), which could be incorporated into the meta-analysis (this trial, however, did not contribute to the subset analyses). None of the individual RCTs had stratified the randomization of patients to the IL-2 vs SOC arms by any of the factors known to affect prognosis (ie, age, ECOG performance status, karyotype, cytological AML subtype, or months from complete remission).

Meta-analysis

Standard meta-analysis methods were used, incorporating all updated IPD that were available (5 of the 6 RCTs).²⁹ A sensitivity analysis was also performed using data from all RCTs, including the trial for which the HRs were available but not the IPD.

All analyses were performed on an intent-to-treat (ITT) basis, including all randomized patients in each trial, according to the treatment assigned by randomization regardless of treatment actually received. There were no “per protocol” analyses.

The endpoints of interest were OS, defined as time from randomization to death from any cause; and LFS, defined as time from randomization to leukemic relapse or death from any cause. These time-related endpoints were analyzed according to Kaplan-Meier methods with stratified log-rank significance testing, using study as the stratification factor. HRs were estimated using Cox regression models stratified by trial (“adjusted HR”) with HR <1 indicating treatment benefit. Cox proportional hazards models were used to check whether the estimates of treatment effects changed after adjustment for known prognostic factors.

Forest plots of HRs were produced for LFS and OS, overall and within subsets according to meaningful trial and patient characteristics. Tests for heterogeneity were performed to assess the statistical significance of observed differences between the treatment effects in different RCTs. Subset

analyses were performed using interaction tests to assess the statistical significance of observed differences between the treatment effects in different subsets.²⁹

Statistical analyses were performed on SAS[®] system version 9.1.3 (SAS Institute, Cary, NC) Graphs were produced using S-Plus[®] version 7.0 (Insightful Corporation, Seattle, WA).

RESULTS

Individual patient data from 449 patients treated with IL-2 and 456 control patients were included in the meta-analysis, plus summary data from 550 patients randomized to IL-2 (n = 276) versus observation (n = 274) in the EORTC-GIMEMA 06991 trial (also known as AML-12).²⁵ Patient demographics for the 5 RCTs for which IPD were available are shown in **Table 2**.²⁰⁻²⁴ Patient characteristics varied slightly from trial to trial; the most notable between-trial difference was age. CCG-2961 was conducted in children (mean age 8.2 years) whereas Blaise and colleagues studied adults whose mean age was ~40 years, similar to that of CALGB 19808 (~43 years). The ALFA 9801 trial included an older population (~60 years of age), and CALGB 9720 enrolled the oldest population (~70 years of age). The mean age of patients enrolled in GIMEMA-EORTC 06991 has not been reported, although eligibility was restricted to patients <61 years of age and the group is presumed to be similar in age to those enrolled in ALFA 9801 and CALGB 19808. Planned doses and schedules of IL-2 administration also differed across trials (**Table 1**). Standardized in units of MIU/m²/month, average (intended) monthly IL-2 doses ranged from 12-24 MIU/m² for 12 months²⁵ to 120 MIU/m² for 2 months.²⁰

Effect on LFS

For IL-2 monotherapy, no significant LFS benefit was observed over controls, either when IPD from 5 RCTs were analyzed or when combining all 6 RCTs (**Figure 1**). The HRs were 0.97 (95% CI: 0.82-1.15; *P* = .74) and 0.96 (95% CI: 0.84-1.10; *P* = .52), based on data from the 5 RCTs or 6 RCTs, respectively. Tests for heterogeneity were also not statistically significant (*P* = .62 and *P* = .74) for the 5 and 6 RCTs, respectively. The Kaplan-Meier LFS curves generated with IPD from the 5 RCTs showed no significant

separation at any point in time (**Figure 2**).

Effect on OS

No significant OS benefit was observed with IL-2 monotherapy over controls, either using IPD from 5 RCTs or from all 6 RCTs (**Figure 3**). The HRs were 1.08 (95% CI: 0.90-1.31; $P = .39$) and 1.06 (95% CI: 0.91-1.24; $P = .46$), based on data from the 5 RCTs or 6 RCTs, respectively. Tests for heterogeneity were also not statistically significant ($P = .54$ and $P = .66$) for the 5 and 6 RCTs, respectively. The Kaplan-Meier OS curves generated from the 5 RCTs with IPD showed no significant separation at any point in time (**Figure 4**).

Subset analyses

Subset analyses are provided using available IPD from RCTs based on age group, gender, karyotype category, AML cytological subtype category, ECOG performance status (0-1 or other) and time from CR (≤ 4 months or > 4 months). Baseline performance status was not available for the Blaise trial nor for CCG 2961; thus, these subset analyses are limited to IPD from 3 trials. A summary of the HRs, together with the significance and interaction testing conducted on all subset analyses is provided in **Table 3**.

No statistically significant differences were found for the effect of IL-2 over controls on either LFS or OS according to age category (< 21 vs 21-60 vs > 60 years), gender (male vs female), ECOG performance status (0-1 vs other), karyotype category (favorable vs intermediate vs unfavorable vs unknown), AML cytological subtype (M0-M5-M6-M7 vs M1-M2-M4 vs other or unknown), or time from CR (≤ 4 months or > 4 months) to initiating maintenance therapy (**Table 3**). Forest plots of these subset analyses are shown in the Appendix (**Supplemental Figures 1-6**). The tests for interaction between the effect of IL-2 and these factors were in all cases far from statistically significant.

DISCUSSION

After AML patients receive induction therapy and if they achieve CR, the duration of their CR1 is a

primary prognostic indicator. Survival duration after relapse depends on various factors,³⁰ but is generally short-lived, with a median of just 5-6 months.¹ Thus, the ability to maintain AML patients in CR1 remains one of the most significant challenges facing hematologists today.

Several multicenter and multinational clinical trials have shown the value of allo-HCT in preventing relapse.³¹⁻³³ However, a major limitation of allo-transplantation is that recognition and elimination of leukemic cells by donor T cells (graft-versus-leukemia reaction, GVL) is also accompanied by destruction of normal host cells (graft-versus-host disease, GVHD), which leads to significant morbidity and mortality.³⁴ Several trials aimed at controlling GVHD by removing donor T cells led to high leukemic relapse rates, which confirmed the major role of activated T cells in leukemic control after allo-HCT.³⁵⁻³⁷ This explains the persistent interest on the part of clinical investigators in IL-2 as a pharmacotherapeutic means of replicating the beneficial effects of allo-transplantation to prevent relapse in AML.

The fundamental premise linking IL-2, a cytokine known to stimulate T- and NK-cell function to destroy leukemic cells, and relapse prevention in AML is compelling from a scientific perspective.^{4,10,38-40} Interest in the role of this cytokine did not subside even after an early RCT failed to demonstrate a significant benefit of IL-2 in survival outcomes in AML patients,²⁰ and several more RCTs ensued.²¹⁻²⁵

Results of these trials are challenging to compare on face value, given the different age groups, remission induction regimens, lengths of follow-up, number of patients discontinuing due to toxicity, and doses of IL-2 that were used. For example, the ALFA 9801 trial²¹ randomized 161 AML patients in CR1 (aged 50-70 years) to 12 months of intermediate dose IL-2 versus observation. Of 77 patients allocated to IL-2, 22 completed 1 year of therapy and no difference in IL-2 versus observation was evident after 3 years of follow-up. CALGB 9720 was a trial in older patients (≥ 60 years) with AML in CR1.²² Eighty-one patients were randomized to low-dose subcutaneous IL-2 therapy, and 66% and 63% subsequently developed Grade 4 thrombocytopenia and neutropenia, respectively. Median LFS and OS were similar for both IL-2 treated patients and controls, leading the authors to conclude that low-dose IL-2 is not a successful strategy for prolonging disease-free survival (DFS) and OS in older AML patients. CALGB

19808²³ evaluated intermediate-dose IL-2 versus observation in 316 AML patients <60 years in CR1 postconsolidation chemotherapy. Ninety days of treatment were planned. Of 107 patients randomized to IL-2, only 47% completed therapy (29% refused after randomization or were unable to start, 28% failed to complete, 11% and 17% had Grade 4 thrombocytopenia and neutropenia, respectively). Median 3-year follow-up revealed a trend in favor of IL-2 for LFS ($P = .11$) and OS ($P = .09$). CCG 2961 was a trial in 289 children with AML²⁴ in which patients received a short course (18 days) of high-dose IL-2 versus no treatment postconsolidation. After a median follow-up of 5 years, there was no difference in DFS or OS between the two regimens. The last trial of IL-2 monotherapy conducted by the EORTC-GIMEMA group began enrolling patients in 1999 and recently reported no difference in LFS or OS at 3 years.²⁵

We conducted these analyses after considering the possibility that the relatively small sample sizes of these trials may have prevented significant results from being detected. Moreover, no subset analyses were possible within the individual RCTs mainly due to sample size restrictions. Because all of these trials had a similar control group of SOC (no treatment), it was possible to carry out this meta-analysis to increase the power of the data previously collected with the goal being to reliably determine the existence of any clinical benefit of IL-2.

The present meta-analysis has some limitations, including the fact that patient populations and doses/schedules of IL-2 varied widely across the trials included. However, the inability to demonstrate significant effects of IL-2 on LFS and OS in all individual trials as well as in all subsets analyzed here makes it unlikely that this treatment, when used as monotherapy for remission maintenance, does provide meaningful benefits. A lack of effect of IL-2 was consistently observed across all subsets of patients grouped by the most important prognostic factors known for AML, namely, age, karyotype category, AML cytological subtype, ECOG performance status, and time from CR to initiation of maintenance therapy. The type of induction therapy, and its potential impact on any benefit of IL-2 maintenance therapy, could not be analyzed here. Gender also had no impact on the lack of difference between IL-2 and controls, consistent with the absence of benefit observed across any other subsets.

An important question remaining is why, given such strong preclinical evidence predicting IL-2

efficacy in AML patients in CR, does IL-2 fail to demonstrate clinical benefit? First, it can be argued that the long term GVL effect, which is well documented after allo-HCT, results from a permanent donor chimerism including a constant activation of antileukemic subclones of donor origin.⁴¹ This situation is obviously not easy to mimic by a relative short-term administration of IL-2 after remission following autologous HCT. Second, it has been proposed that the efficacy of IL-2 monotherapy could be hampered by the activity of other immune cells that prevent activation and proliferation of cytotoxic lymphocytes, ie, the effector cells of IL-2.² Reactive oxygen species (ROS) or “oxygen radicals” derived from adjacent phagocytic cells have been shown to inhibit the ability of IL-2 to effectively activate T and NK cells.⁴² The ROS also reduce expression of the CD3 ζ antigen critical to signal transduction in lymphocytes⁴³⁻⁴⁵ and trigger apoptosis of cytotoxic lymphocytes.⁴⁶⁻⁴⁸ Several preclinical studies (reviewed in Romero et al. {Romero, 2009 93795 /id}) have established a role for histamine dihydrochloride (HDC) in AML. When added to immunotherapy with IL-2, HDC inhibits ROS production, mediated by H₂-receptors on myeloid cells, and may help maintain viability and function of anti-leukemic lymphocytes. Clinical pharmacodynamic data from a Phase 2 trial in AML patients demonstrated that HDC protected the effects of IL-2 on T and NK-cells with encouraging clinical results. {Brune, 1996 78460 /id; Hellstrand, 1997 78638 /id} In a subsequent randomized trial of AML patients in CR (n=320) {Brune, 2006 77599 /id} remission maintenance therapy with HDC in conjunction with low-dose IL-2 resulted in a significant prolongation of LFS ($P<0.01$) and a trend toward improvement in OS in patients in first CR ($P=0.12$). {Brune, 2006 77599 /id} Thus, the notion that IL-2 has the potential to improve LFS as well as OS in AML may be correct, but for IL-2 to exert a significant clinical effect on relapse prevention in this disease, its activity on T and NK cells may need to be protected from interference by ROS.²

In conclusion, this meta-analysis confirms that IL-2, when given as monotherapy, is not effective as a remission maintenance therapy for AML patients in CR1, a conclusion also reached by others based on data extracted from the literature.⁴⁹ However, the optimism that clinicians once held for immunotherapy to prevent relapse in AML should not be discounted, as it may be possible to protect the activity of IL-2 on T- and NK-cells from ROS-mediated destruction in the tumor microenvironment.^{27,39,50}

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Table 1. Randomized trials of IL-2 monotherapy versus no treatment (SOC) as remission maintenance in AML patients in CR1

Trial (NCT)^a	n	Median follow-up (months)	Age (yrs)	IL-2 regimen	Planned monthly dose (MIU/m²) x no. of months	Results, IL-2 vs controls^b	P-values, IL-2 vs controls
1. Blaise et al 2000 ²⁰	78	80	<50	Cycle 1: 12 MIU/m ² QD x 5 days followed by 4 cycles of 2 days each	120 x 2	7-yr LFS: 30% vs 36% 7-yr OS: 38% vs 47%	LFS <i>P</i> = .54 OS <i>P</i> = .65
2. ALFA 9801 ²¹	161	40	50-70	5 MIU/m ² QD x 5 days/month	25 x 12	4-yr EFS ^c : 28% vs 32% 4-yr OS: 41% vs 47%	EFS <i>P</i> = .88 OS <i>P</i> = .14
3. CALGB 9720 ²² (NCT00003190)	163	100	≥60	0.9 MIU/m ² QD x 10-14 days; followed by pulses of 12 MIU/m ² QD x 3 days between each 14-day cycle	82 x 3	No difference in median LFS = 6.1 months No difference in median OS = 14.7 months	LFS <i>P</i> = .47 OS <i>P</i> = .61
4. CALGB 19808 ²³ (NCT00006363)	214	69	<60	1 MIU/m ² QD x 10-14 days; followed by pulses of 12-15 MIU/m ² QD x 3 days between each 14-day cycle	91 x 3	3-yr LFS: 56% vs 45% 3-yr OS: 68% vs 61%	LFS <i>P</i> = .11 OS <i>P</i> = .09

Trial (NCT)^a	n	Median follow-up (months)	Age (yrs)	IL-2 regimen	Planned monthly dose (MIU/m²) x no. of months	Results, IL-2 vs controls^b	P-values, IL-2 vs controls
5. CCG-2961 ²⁴ (NCT00002798)	289	54	≤21	9 MIU/m ² QD x 4 days then 1.6 MIU/m ² QD days 8-17 (14 infusions total)	52 x 0.6	5-yr LFS: 51% vs 58% 5-yr OS: 70% vs 73%	LFS <i>P</i> = .49 OS <i>P</i> = .73
6. EORTC- GIMEMA 6991 ²⁵ (NCT00004128)	550	43	<61	2.3 to 4.6 MIU/m ² QD x 5 days/month	12-24 x 12	3-yr LFS: 44% vs 42% 3-yr OS: 54% vs 56%	LFS <i>P</i> = .57 OS <i>P</i> = .94

^aClinicalTrials.gov registry number if available.

^bIL-2 versus SOC (no treatment).

^cEFS = event free survival calculated as the date from randomization to the date of complete remission achievement failure, first relapse, or death.

LFS = leukemia-free survival; OS = overall survival; QD = once daily; SOC = standard-of-care.

Table 2. Distribution of baseline patient characteristics in the 5 IPD trials of IL-2 alone versus control (no treatment)

Baseline	Blaise et al ²⁰		ALFA 9801 ²¹		CALGB 9720 ²²		CALGB 19808 ²³		CCG-2961 ²⁴	
characteristics at diagnosis^a										
Treatment (n)	IL-2 (40)	Control (38)	IL-2 (77)	Control (84)	IL-2 (81)	Control (82)	IL-2 (107)	Control (107)	IL-2 (144)	Control (145)
Age, years, mean (SD)	38.9 (12.1)	41.2 (11.4)	60.6 (5.3)	59.6 (5.3)	69.3 (5.6)	69.5 (5.9)	43.3 (10.6)	42.9 (10.7)	8.0 (5.4)	8.4 (5.7)
Gender, n, M/F	22/18	17/21	40/37	43/41	41/40	52/30	50/57	62/45	89/55	67/78
ECOG PS, n	NA	NA							NA	NA
0			23	25	30	29	44	44		
1			40	49	40	34	52	48		
2			10	6	8	14	6	8		
3			3	0	2	1	2	2		
Karyotype^b, n										
Favorable	8	9	4	14	13	19	32	33	26	26
Intermediate	17	17	56	53	38	39	52	52	55	44
Unfavorable	0	2	7	9	10	7	7	3	1	2
AML subtype^c, n										
M0-M5-M6-M7	9	7	25	24	17	18	19	15	44	46
M1-M2-M4	30	24	52	60	60	60	81	84	99	94

Baseline characteristics at diagnosis^a	Blaise et al²⁰	ALFA 9801²¹	CALGB 9720²²	CALGB 19808²³	CCG-2961²⁴					
Months from CR, mean (SD)	3.5 (0.9)	3.5 (1.1)	4.3 (0.9)	4.2 (1.7)	2.2 (0.9)	2.3 (1.0)	5.1 (1.4)	5.2 (1.7)	4.2 (1.3)	4.4 (1.7)

^aBased on ITT.

^bFavorable, intermediate, and unfavorable karyotypes were defined as in each trial.^{20-24,28}

^cSeven M3 patients entered in the trial by Blaise et al²⁰ have been excluded from this grouping of histological subtypes.

ECOG PS = Eastern Cooperative Oncology Group performance status; NA = data not available; SD = standard deviation

Table 3. Summary of effects of IL-2 monotherapy on LFS and OS in various subsets^a

Strata	LFS			OS		
	Subset HR (95% CI)	Test of treatment effect in subset	Test of treatment by subset interaction	Subset HR (95% CI)	Test of treatment effect in subset	Test of treatment by subset interaction
Age <21 years	1.11 (0.78, 1.57)	<i>P</i> = .56		1.05 (0.68, 1.64)	<i>P</i> = .82	
Age 21-60 years	0.93 (0.71, 1.22)	<i>P</i> = .61	<i>P</i> = .69	0.99 (0.73, 1.35)	<i>P</i> = .95	<i>P</i> = .75
Age >60 years	0.93 (0.71, 1.22)	<i>P</i> = .59		1.16 (0.88, 1.54)	<i>P</i> = .29	
Male	0.93 (0.74, 1.17)	<i>P</i> = .54		1.05 (0.81, 1.35)	<i>P</i> = .72	
Female	1.02 (0.80, 1.32)	<i>P</i> = .85	<i>P</i> = .58	1.17 (0.88, 1.56)	<i>P</i> = .28	<i>P</i> = .57
ECOG PS 0-1	0.88 (0.71, 1.10)	<i>P</i> = .27		1.11 (0.87, 1.41)	<i>P</i> = .40	
ECOG PS other	0.95 (0.55, 1.64)	<i>P</i> = .87	<i>P</i> = .79	0.96 (0.53, 1.76)	<i>P</i> = .90	<i>P</i> = .46
Karyotype favorable	0.84 (0.54, 1.29)	<i>P</i> = .42		0.98 (0.59, 1.63)	<i>P</i> = .94	
Karyotype intermediate	1.05 (0.83, 1.33)	<i>P</i> = .68	<i>P</i> = .40	1.12 (0.86, 1.46)	<i>P</i> = .39	<i>P</i> = .80
Karyotype unfavorable	0.58 (0.28, 1.18)	<i>P</i> = .13		0.86 (0.41, 1.80)	<i>P</i> = .69	
Karyotype unknown	0.93 (0.66, 1.30)	<i>P</i> = .65		0.93 (0.63, 1.35)	<i>P</i> = .69	

Strata	LFS			OS		
	Subset HR (95% CI)	Test of treatment effect in subset	Test of treatment by subset interaction	Subset HR (95% CI)	Test of treatment effect in subset	Test of treatment by subset interaction
AML subtype M0-M5-M6-M7	0.98 (0.70, 1.36)	$P = .88$		0.90 (0.62, 1.31)	$P = .60$	
AML subtype M1-M2-M4	1.00 (0.82, 1.23)	$P = .97$	$P = .58$	1.21 (0.97, 1.52)	$P = .09$	$P = .24$
AML subtype other or unknown	0.57 (0.20, 1.61)	$P = .29$		0.64 (0.22, 1.82)	$P = .40$	
Months from CR \leq 4 months	0.94 (0.76, 1.16)	$P = .56$		1.09 (0.87, 1.38)	$P = .46$	
Months from CR $>$ 4 months	1.08 (0.82, 1.42)	$P = .60$	$P = .43$	1.12 (0.81, 1.55)	$P = .49$	$P = .90$

^aSee online Appendix for forest plots of subset analyses.

CI = confidence interval; CR = complete remission; ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; LFS = leukemia-free survival; OS = overall survival.

FIGURE LEGENDS

Figure 1. Forest plots of HRs for the benefit of IL-2 monotherapy in terms of leukemia-free survival in all 6 RCTs.

CI = confidence interval; HR = hazard ratio; IL-2 = interleukin-2; O/N = event rate per arm where O is the number of observed events (relapse or death) and N is the sample size; RCTs = randomized controlled trials.

Figure 2. Kaplan-Meier estimates of leukemia-free survival using individual patient data from 5 RCTs of IL-2 monotherapy versus control (no treatment).

IL-2 = interleukin-2; RCTs = randomized controlled trials.

Figure 3. Forest plots of HRs for the benefit of IL-2 monotherapy in terms of overall survival in all 6 RCTs.

CI = confidence interval; HR = hazard ratio; IL-2 = interleukin-2; O/N = event rate per arm where O is the number of observed events (relapse or death) and N is the sample size; RCTs = randomized controlled trials.

Figure 4. Kaplan-Meier estimates of overall survival using individual patient data from 5 RCTs of IL-2 monotherapy versus control (no treatment).

IL-2 = interleukin-2; RCTs = randomized controlled trials.