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The prophylactic use of granulocyte-colony stimulating factor during remission induction is associated with increased leukaemia-free survival of adults with acute lymphoblastic leukaemia: A joint analysis of five randomised trials on behalf of the EWALL

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ABSTRACT

Background: Granulocyte-colony stimulating factor (G-CSF) is used to prevent febrile neutropenia and support intense chemotherapy. However, its impact on long-term outcome in oncological patients including adults with acute lymphoblastic leukaemia (ALL) has not been determined so far.

Methods: In the current study follow-up data from individual patients recruited in five multicentre, prospective, randomised trials were pooled to perform a joint analysis. Among 347 adults and adolescents with ALL, 185 were assigned to receive prophylactically G-CSF along with induction chemotherapy while 162 patients were treated without G-CSF support.

Results: With the median follow-up of 5.3 years, there was a tendency towards increased 5 year probability of the overall survival for the G-CSF arm compared to the controls (32% ± 4% versus 23% ± 4%, $p = .07$), which reached statistical significance in a subgroup of T-ALL (51% ± 8% versus 29% ± 9%, $p = .01$) and among patients aged 21–40 years (44% ± 6% versus 27% ± 6%, $p = .03$). The probability of leukaemia-free survival was 38% ± 4% and 24% ± 4% ($p = .01$) while the median remission duration equalled 33 and

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17 months (p = .007), respectively. In a multivariate analysis the prophylactic use of G-CSF was independently associated with reduced risk of relapse (hazard ratio (HR) = .64, p = .007) and treatment failure (HR = .67, p = .02).

Conclusions: The prophylactic use of G-CSF during induction of ALL is associated with improved long-term outcome and should be recommended especially in a setting of T-ALL and in 'young adults'. Our analysis provides the first direct evidence coming from prospective trials for the impact of primary G-CSF prophylaxis on disease-free survival of oncological patients.

1. Introduction

Granulocyte-colony stimulating factors (G-CSF), either filgrastim or lenograstim are widely used as a prophylaxis of febrile neutropenia. Appropriate guidelines have been published by the European Organisation for Research and Treatment of Cancer[1] and the American Society of Clinical Oncology.[2] The primary prophylaxis was proven to reduce the risk of febrile neutropenia, shorten the time and need for hospitalisation and reduce administration of intravenous antibiotics.[3–6] However, no direct evidence from prospective clinical trials has been provided so far to prove the impact of G-CSF prophylaxis on long-term outcome.

The guidelines have been elaborated based mainly on data from patients with solid tumours and lymphomas treated usually with repeated courses of the same chemotherapy regimens.[1,2] In case of acute lymphoblastic leukaemia (ALL) the therapy consists of remission induction, followed by consolidation and either maintenance or hematopoietic stem cell transplantation (HSCT). The first two phases include intensive multi-agent chemotherapy resulting in profound and long-lasting neutropenia. In addition, the disease itself usually presents with pancytopenia. Hence, the induction–consolidation therapy is associated with high risk of infections, which provides strong rationale for the use of G-CSF.

The prophylactic administration of G-CSF in adults with ALL was a subject of seven multicentre, prospective, randomised trials conducted mainly in the last decade of the XXth century, with study populations ranging from 51 to 198 patients.[7–12] The primary end-point of all studies was to evaluate the impact of G-CSF treatment on neutrophil recovery and the rate of infections. In contrast, the populations were too small and the follow-up too short to assess the role of G-CSF prophylaxis in the context of survival.

In the current analysis, performed on behalf of the European Group for Adult Acute Lymphoblastic Leukemia we pooled individual patient data from five European randomised trials where G-CSF was administered in the first course of remission induction. Whenever possible, the observation of patients was updated. Our goal was to assess the impact of G-CSF prophylaxis on long-term outcome of adults and adolescents with ALL.

2. Patients and methods

2.1. Design and early results of clinical trials included in the joint analysis

The analysis included data from five prospective, controlled, randomised clinical trials recruiting patients between 1990 and 2002.[9–12] In four studies lenograstim was used as the G-CSF prophylaxis while in the remaining one filgrastim was administered. In the control arms patients did not receive growth factors except for the treatment of severe infectious complications. In all trials induction regimen consisted of repeated doses of anthracycline and vincristin accompanied by continues administration of steroids. In addition, according to particular protocols patients received either asparaginase or cyclophosphamide. Design of particular trials as well as early results are presented in Table 1.

2.2. Patients

Altogether 347 patients were included in the current analysis out of 350 individuals recruited to the five trials. In the remaining three cases the data on survival were insufficient. The median age of 213 males and 134 females was 33 years (range, 15–91 years). The proportion of B-cell and T-cell ALL was 74% and 26%, respectively. In 66 out of 287 evaluable patients (23%), Philadelphia chromosome was detected either by cytogenetic analysis of t(9, 22) or molecular analysis of BCR/ABL fusion gene.

One-hundred-eighty-five patients received G-CSF prophylaxis, while 162 patients were assigned to the control arms. As presented in Table 2 the clinical characteristics of both groups was comparable, except for a tendency for higher proportion of adolescents, as defined by the age equal or lower than 20 years in the control arm compared to the G-CSF arm (23% versus 18%, p = .12).

2.3. Statistical methods

Individual patient data from five study groups were collected and pooled to create a common database. Observations from the Austrian, Polish and Swedish trial were updated compared to initial reports.

Table 1 – Design and early results of five randomised trials assessing the prophylactic use of granulocyte-colony stimulating factor (G-CSF) in adults with acute lymphoblastic leukaemia included in a joint analysis.

Study	Austrian (Ref. 9)	PALG 4-96 (Ref. 10)	GET-LALA Trial 1 (Ref. 11)	GET-LALA Trial 2 (Ref. 11)	Swedish (Ref. 12)
N	51	64	107[a]	62[a]	66
Median age, range (years)	42 (16–79)	27 (16–58)	30 (15–55)	36 (17–55)	47 (16–79)
Study design					
Type of G-CSF	Filgrastim 5 μg/kg	Lenograstim 150 μg/m^2	Lenograstim 263 μg	Lenograstim 263 μg	Lenograstim 5 ug/kg
Time of G-CSF administration	Induction I, since day 2 until ANC recovery	Induction, days 2–6, 9–13, 16–20, 23 until ANC recovery Consolidation, days 39–49, 61–71	Induction, since day 9 or 16 until ANC recovery	Induction, since day 4 until ANC recovery	Induction, days 3–14, 17–28
Results (compared to controls)					
Duration of neutropenia	Shorter	Shorter	No effect	Shorter	–
Rate of febrile neutropenia	Reduced	Reduced	–	–	–
Rate of infections	Reduced	Reduced	No effect	Reduced	No effect
Adherence to chemotherapy protocol	–	Shorter duration of induction–consolidation	–	–	–

Total doses of intravenous chemotherapy administered in particular protocols were as follows:
Austrian: INDUCTION I: DNR 180 mg/m^2, VCR 6 mg/m^2, ASP 35,000 U/m^2, PDN 1680 mg/m^2; INDUCTION II: CP 1950 mg/m^2, ARA-C 1200 mg/m^2, MP 1680 mg/m^2; CONSOLIDATION: DOXO 100 mg/m^2, VCR 6 mg/m^2, DEXA 280 mg/m^2, MP 420 mg/m^2, CP 650 mg/m^2, ARA-C 600 mg/m^2, TG 840 mg/m^2.
PALG 4-96: INDUCTION: EPI 240 mg/m^2, VCR 6 mg/m^2, ASP 48,000 U/m^2, PDN 1680 mg/m^2; CONSOLIDATION: MTX 1000 mg/m2, VEP 200 mg/m2, MP 1550 mg/m^2, CP 1300 mg/m^2, ARA-C 12 g/m^2.
GET-LALA Trial 1 and 2: INDUCTION: DNR 150 mg/m^2 or IDA 36 mg/m^2, VCR 8 mg, PDN 840 mg/m^2, CP 1500 mg/m^2; CONSOLIDATION: various modalities.
Swedish: INDUCTION: DOXO 60 mg/m2, VCR 7.5 mg/m2, PDN 1680 mg/m2; CONSOLIDATION: MTX 225 mg/m^2, ARA-C 1440 mg/m^2, TG 120 mg/m^2, ASP 2800 U/kg, CP 1200 mg/m^2.
DNR, daunorubicin; VCR, vincristin; ASP, L-asparaginase; PDN, prednisone; CP, cyclophosphamide; ARA-C, cytosine arabinoside; DOXO, doxorubicin; DEXA, dexamethasone; MP, mercaptopurine; TG, thioguanine; EPI, epirubicin; MTX, methotrexate; VEP, etoposide; IDA, idarubicin.

[a] There was a third arm in GET-LALA trials, where patients achieved granulocyte–macrophage colony stimulating factor. These patients are not included in the current analysis.

Table 2 – Patient characteristics.

	Granulocyte-colony stimulating factor (G-CSF) (N = 185)	Control (N = 162)	p
Age (years)	32 (15–79)	35 (16–91)	.97
Age ⩽20 years	31 (18%)	36 (23%)	.12
Age ⩾60 years	11 (6%)	14 (9%)	.33
Gender (male/female)	113 (61%)/72 (39%)	100 (62%)/62 (38%)	.9
Immune phenotype (B-cell/T-cell)[a]	119 (74%)/42 (26%)	108 (77%)/33 (23%)	.59
WBC ($\times 10^9$/L)[b]	12 (1–513)	16 (1–860)	.39
WBC $>30 \times 10^9$/L	57 (34%)	52 (37%)	.62
Ph and/or BCR/ABL – positive[c]	33 (21%)	33 (25%)	.38
Risk group (standard/high)[d]	54 (42%)/74 (58%)	41 (39%)/64 (61%)	.63

[a] Unknown for 24 patients in the G-CSF group and 21 in controls.
[b] Unknown for 17 patients in the G-CSF group and 21 in controls.
[c] Unknown for 18 patients in the G-CSF group and 20 in controls.
[d] In the PALG 4-96 trial features associated with high risk were: age >35 years, pro-B or pre-T phenotype, WBC $>30 \times 10^9$/L, t(9;22), two induction courses required for complete remission; in the GET-LALA trials high risk was: B-cell ALL with $CD10^-CD20^-CD19^-$ phenotype, myeloid phenotypic markers, WBC $>30 \times 10^9$/L, t(9;22), t(4;11), t(1;19), B-cell or T-cell ALL requiring for two courses of induction; in the Austrian and Swedish trials risk groups were not assigned.

The probability of the overall survival (OS) at 5 years was the primary study end-point. Secondary end-points were: the probabilities of leukaemia-free survival (LFS) remission duration (RD), early mortality (EM) and the rate of complete remission (CR). The OS was defined as time from randomisation to death from any cause. LFS was calculated since date of CR until either relapse or death in remission, while RD was time from CR to relapse. All OS, LFS and RD were estimated using the Kaplan–Meier method.[13] Both study groups were compared with respect of these parameters using the log rank test.

EM was defined as death from any cause within 8 weeks since start of induction therapy. The comparison of EM and CR rates as well as patient characteristics with regard to categorical variables was done with the use of chi^2 test, while for numerical variables U Man–Whitney test was applied.

Table 3 – Long-term outcome according to the prophylactic administration of granulocyte-colony stimulating factor (G-CSF).

	n	OS at 5 years, %	OS, median (months)	p	LFS at 5 years, %	LFS, median (months)	p	RD at 5 years, %	RD, median (months)	p
All patients				.07			.01			.007
G-CSF	185	32 (±4)	24		38 (±4)	25		42 (±5)	33	
Control	162	23 (±4)	20		24 (±4)	13		27 (±4)	17	
B-ALL				.4			.21			.11
G-CSF	119	29 (±4)	18		30 (±5)	16		35 (±5)	23	
Control	108	21 (±4)	19		21 (±5)	16		23 (±5)	17	
T-ALL				.01			.004			.01
G-CSF	42	51 (±8)	61		57 (±8)	66		57 (±8)	Not reached	
Control	33	29 (±9)	21		23 (±8)	12		17 (±9)	13	
Age ⩽20 years				.96			.95			.87
G-CSF	31	38 (±9)	25		31 (±9)	15		35 (±9)	20	
Control	38	34 (±8)	22		34 (±9)	18		35 (±9)	18	
Age 21–40 years				.03			.0009			.001
G-CSF	84	44 (±6)	40		54 (±6)	86		55 (±6)	88	
Control	63	27 (±6)	21		20 (±6)	13		22 (±7)	16	
Age 41–60 years				.65			.45			.39
G-CSF	58	16 (±5)	20		18 (±6)	16		25 (±8)	23	
Control	46	14 (±6)	19		18 (±7)	12		22 (±8)	14	
Age >60 years				.55			.61			.61
G-CSF	10	10 (±9)	10		86 (±13)	Not reached		86 (±13)	Not reached	
Control	14	7 (±7)	5		40 (±30)	17		40 (±30)	17	
Standard risk				.63			.35			.11
G-CSF	54	34 (±7)	25		34 (±7)	17		39 (±8)	28	
Control	41	27 (±8)	26		22 (±7)	17		22 (±7)	17	
High risk				.5			.29			.31
G-CSF	74	29 (±6)	23		35 (±7)	18		41 (±7)	26	
Control	64	26 (±6)	20		23 (±6)	12		29 (±8)	14	

OS, overall survival; LFS, leukaemia-free survival; RD, remission duration.
Data on survival are presented as Kaplan–Meier estimates at 5 years ± standard error.

The effect of G-CSF administration on OS, LFS and RD was verified in a multivariate Cox proportional hazard model[14] adjusted for age, leukocyte count, and the presence of Philadelphia chromosome.

All statistical tests were two-sided and differences with p value <.05 were considered statistically significant.

3. Results

3.1. *Impact of G-CSF prophylaxis on outcome in the whole study group*

The CR rate for the whole study population equaled 84% and did not differ for patients receiving G-CSF and the control group (86% versus 81%, $p = 0.2$). Eight patients (4.2%) died within 8 weeks since start of induction in the G-CSF arm while 10 patients (6.2%) in the control arm ($p = .78$).

With the median follow-up of 5.3 years the probability of the OS at 5 years for the whole study group equaled 28% (standard error, ±3%). There was a tendency towards increased OS rate for the G-CSF arm compared to the controls (32% ± 4% versus 23% ± 4%, $p = .07$). The median OS was 24 and 20 months, respectively (Table 3, Fig. 1A). Twenty patients (11%) in the G-CSF arm and 15 (9%) in the control arm were treated with allogeneic HSCT in the first CR. Proportions of autologous transplantations were 28 (15%) and 25 (15%), respectively. When observations were censored at the time of allogeneic HSCT the 5-year probabilities of the OS were 29% ± 4% for the G-CSF arm and 22% ± 4% for the controls ($p = .16$). In a multivariate analysis adjusted to other potential prognostic factors, the prophylactic administration of G-CSF was associated with decreased risk of the overall mortality, however, the effect did not reach statistical significance (hazard ratio (HR) = 0.78, 95% confidence interval (CI) = 0.6–1.03, $p = .08$) (Table 4). The risk of mortality was independently affected by increasing age, initial WBC >30 × 10^9/L, and the presence of Philadelphia chromosome.

The probability of the LFS at 5 years was 32% ± 3% for the whole group and was significantly higher in the G-CSF arm than in controls (38% ± 4% versus 24% ± 4%, $p = .01$) with the median LFS of 25 and 13 months, respectively (Table 3, Fig. 1B). The difference remained significant after censoring the observations at the time of allogeneic HSCT: 32% ± 4% versus 19% ± 4%, $p = .04$. In the Cox model the use of G-CSF prophylaxis was the only independent factor associated with reduced risk of treatment failure, either relapse or non-relapse mortality (HR = 0.69, 95% CI = 0.51–0.93, $p = 0.02$) (Table 4).

The probability of maintaining CR at 5 years was 36% ± 3% in the entire study population. The RD was significantly prolonged for patients receiving G-CSF prophylaxis compared to the controls with the median RD of 33 and 17 months, respectively, and 5-year probabilities of 42% ± 5% versus 27% ± 4%, respectively, $p = .007$ (Table 3, Fig. 1C). The effect remained significant in the analysis censored at the time of allogeneic HSCT: 41% ± 5% versus 23% ± 4%, $p = .006$. Results of the multivariate analysis including other potential prognostic factors revealed G-CSF prophylaxis to be the only factor independently affecting the risk of relapse (HR = 0.64, 95% CI = 0.46–0.88, $p = .007$) (Table 4).

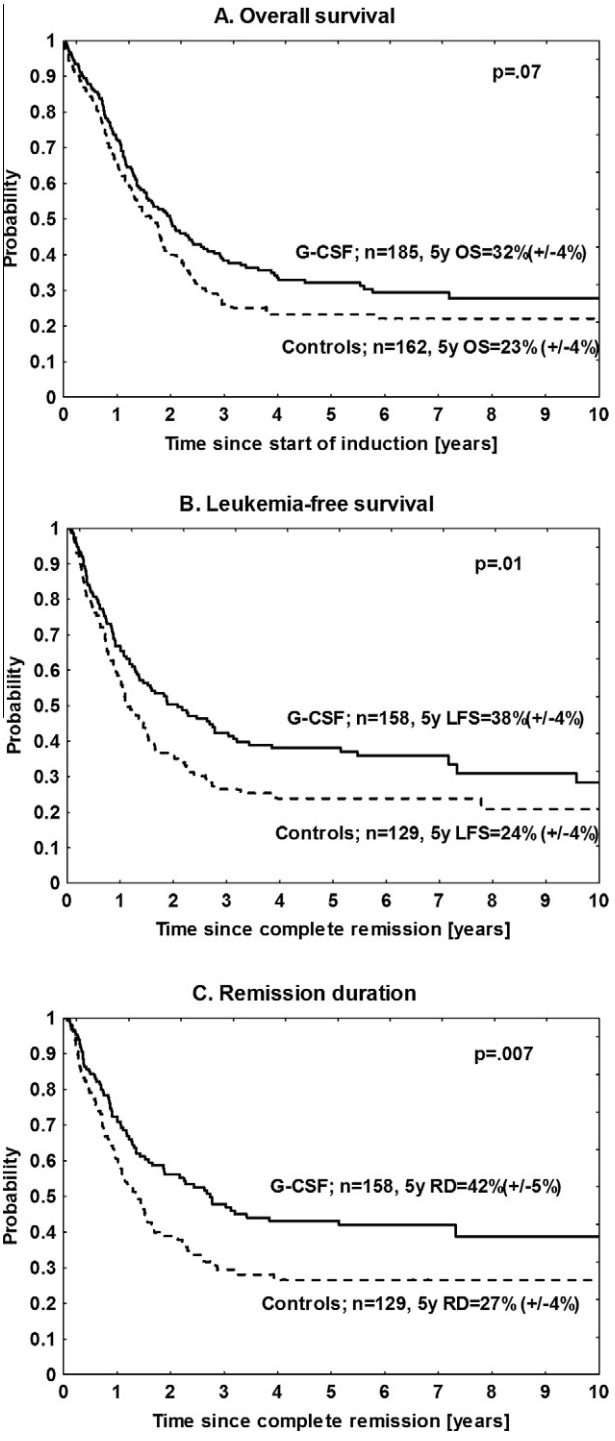

Fig. 1 – Long-term outcome of adults and adolescents with acute lymphoblastic leukaemia according to prophylactic administration of granulocyte-colony stimulating factor (G-CSF) during remission induction.

3.2. *Impact of G-CSF prophylaxis on outcome in B-cell and T-cell ALL*

The impact of G-CSF prophylaxis on long-term outcome was separately analysed according to ALL immune phenotype. In the B-cell ALL subgroup the treatment arms did not differ significantly with regard to the probabilities of the OS and

Table 4 – Multivariate analysis of factors associated with long-term outcome.

	HR (±95% CI)	p
Mortality		
G-CSF prophylaxis	0.78 (0.6–1.03)	0.08
Age, years (continues variable)	1.018 (1.009–1.026)	<0.0001
WBC $>30 \times 10^9$/L	1.4 (1.05–1.89)	0.02
Ph and/or BCR/ABL – positivity	1.47 (1.19–1.82)	0.0002
Treatment failure (either relapse or non-relapse mortality)		
G-CSF prophylaxis	0.69 (0.51–0.93)	0.02
Age, years (continues variable)	1.004 (0.995–1.014)	0.34
WBC $>30 \times 10^9$/L	1.32 (096–1.81)	0.09
Ph and/or BCR/ABL – positivity	1.19 (0.93–1.52)	0.16
Relapse		
G-CSF prophylaxis	0.64 (0.46–0.88)	0.007
Age, years (continues variable)	1.007 (0.996–1.017)	0.22
WBC $>30 \times 10^9$/L	1.25 (0.88–1.76)	0.21
Ph and/or BCR/ABL – positivity	1.25 (0.94–1.64)	0.12

Data are presented as hazard ratio (HR) ±95% confidence interval (CI).

LFS (Table 4). However, there was a tendency to prolonged RD for patients receiving G-CSF prophylaxis compared to the remaining ones with the median RD of 23 versus 17 months ($p = .11$).

In contrast, in the T-cell ALL subgroup the use of G-CSF prophylaxis was associated with significantly improved OS, LFS, and RD (Table 3, Fig. 2). The median OS was prolonged from 21 months in the control arm to 61 months in the G-CSF arm ($p = .01$), while the median LFS was 12 and 66 months, respectively ($p = .004$). The median RD was 13 months in the control arm while it was not reached in patients receiving G-CSF prophylaxis after 10 years follow-up ($p = .01$).

3.3. *Impact of G-CSF prophylaxis on outcome according to age*

The effect of prophylactic administration of G-CSF on long-term outcome was analysed in subgroups according to age, including 'adolescents' (⩽20 years), 'young adults' (21–40 years), 'seniors' (41–60 years), and 'elderly patients' (>60 years). The only significant differences were found for 'young adults' where G-CSF prophylaxis was associated with prolonged OS (median 44 versus 27 months, $p = .03$), LFS (median 86 versus 13 months, $p = .0009$) and RD (median 88 versus 16 months $p = .001$) (Table 3).

4. Discussion

ALL is considered one of the most aggressive neoplasms with natural history leading to death within few months. On the other hand it is usually chemosensitive and potentially curable with intensive chemotherapy protocols. According to recently published studies CR may be achieved in approximately 80–90% of patients, however, long-term survival rarely exceeds 50%.[15] The reason of failure of induction treatment is either disease resistance or treatment-related complications, mainly neutropenic infections. Late mortality is most frequently a consequence of the disease recurrence.

In a setting of patients with lymphoma and solid tumours a meta-analysis of 13 randomised trials including 3122 patients documented that the prophylactic use of G-CSF was associated with reduced risk of febrile neutropenia and statistically significant reduction of early mortality from 5.7% to 3.4%.[5] Even then, however, no direct evidence with regard to long-term outcome could be provided. With regard to ALL the impact of G-CSF prophylaxis on infectious complications was demonstrated by three trials, [9–11] while two others[7,8] failed to show significant differences. In our joint analysis, despite high intensity of induction chemotherapy, the EM was generally low with the difference of 2% in favour of the G-CSF arm, not reaching statistical significance. It must be stressed, however, that in contrast to lymphoma and solid tumour patients all individuals in our analysis were treated as inpatients with the facilities for anti-infectious prophylaxis, early detection and therapy. Hence, our findings suggest that appropriate supportive treatment may overcome the benefit of G-CSF prophylaxis in terms of EM in a setting of ALL. On the other hand, statistical power of the analysis was much lower compared to the meta-analysis by Kuderer et al.[5]

Despite marginal difference with regard to the EM, we observed a tendency towards improved OS of patients administered G-CSF during induction. The potential survival advantage was hence dependent on rather late than early events. Indeed, we found significantly reduced risk of relapse among patients receiving G-CSF with median remission duration prolonged by 16 months and the median LFS prolonged by 12 months for patients treated with G-CSF prophylaxis. The most probable explanation of this phenomenon is that G-CSF prophylaxis enabled better compliance to chemotherapy protocols, thus allowing maintenance of dose-density and dose-intensity. Although we were not able to study this aspect in a joint analysis, according the initial report of the PALG 4-96 study, patients receiving G-CSF experienced significantly less treatment delays and completed the entire induction–consolidation protocol 19 days earlier than patients assigned to the control arm.[10] Similarly, in a study by Ottmann et al.[8] not included in the current analysis, G-CSF administered along with the second course of induction was associated with less frequent prolonged interruptions of chemotherapy administration and significantly earlier completion of the whole protocol. In the Austrian, French, and Swedish studies this issue has not been investigated in details. Evidence supporting the hypothesis may also be derived from the literature, where G-CSF has been documented to maintain relative dose intensity in a meta-analysis of solid tumours and lymphomas[3,5,16] as well as in a single prospective study on patients with aggressive non-Hodgkin lymphoma.[17] Furthermore, retrospective data indicate that relative dose intensity influence survival, in particular among patients with aggressive lymphoma.[18,19]

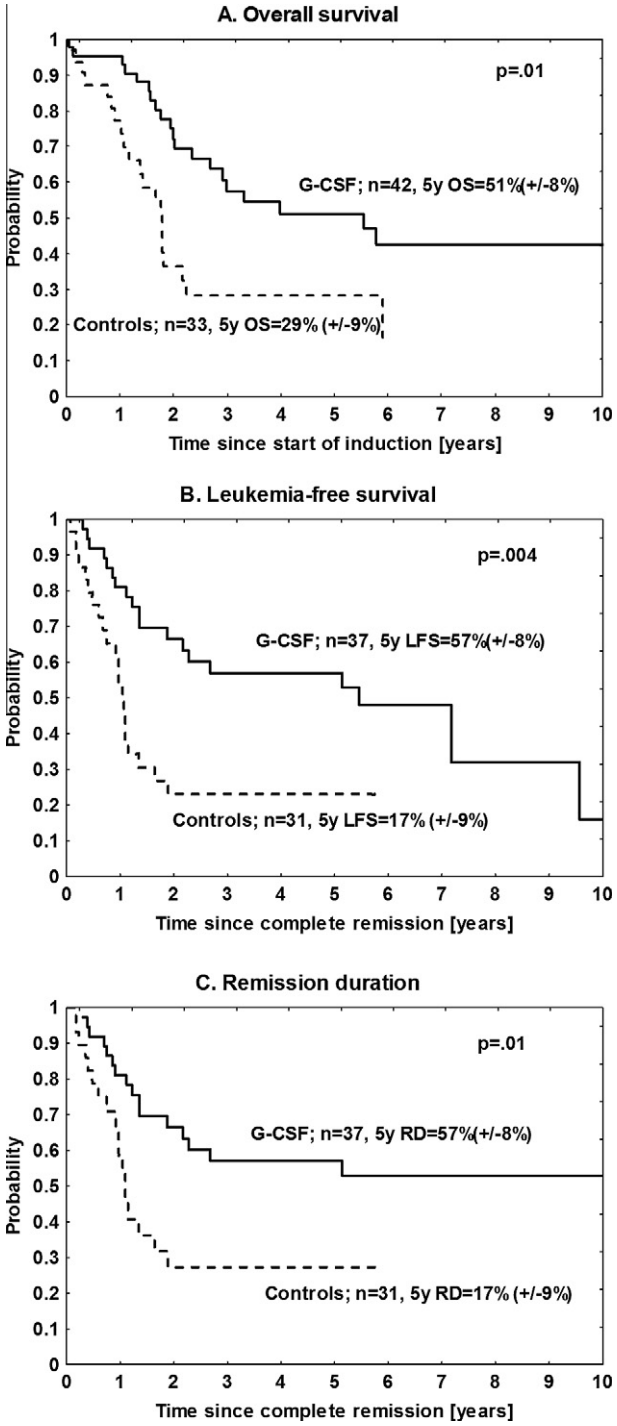

Fig. 2 – Long-term outcome of adults and adolescents with T-cell acute lymphoblastic leukaemia according to prophylactic administration of granulocyte-colony stimulating factor (G-CSF) during remission induction.

The issue of dose intensity and dose density is emerging in the field of ALL. Multiple retrospective studies showed that the probability of OS and LFS was markedly improved for adolescents treated according to paediatric compared to adult-like protocols.[20–24] Paediatric regimens were characterised by higher doses of cytostatics, while their conduct was characterised by less deviations resulting in increased absolute and relative dose intensity. These observations indicate that maintaining intensity of chemotherapy in ALL may be essential in the context of long-term outcome and possibly more important in a setting of ALL than in case of other malignancies. It could therefore explain why the impact of G-CSF prophylaxis on disease-free survival could be demonstrated in our cohort, while not in previous prospective analyses on patients with lymphomas and solid tumours.

Results of our analysis provide strong argument to recommend the prophylactic use of G-CSF in adults with ALL. However, our findings suggest that the benefit may vary according to the disease subtype and may be more pronounced in a subgroup of patients with T-lineage disease. Indeed in this subgroup the impact of G-CSF administration on LFS and RD was dramatic and translated into significant improvement in the OS, which was prolonged by 40 months. It may only be speculated that maintaining the treatment intensity is especially critical in case of T-lineage ALL, which used to be considered a more aggressive subtype.

The impact of G-CSF prophylaxis may also vary according to patient's age. Results of the CALGB 9111 Study[7] suggested that elderly patients may particularly benefit from the use of G-CSF with markedly increased chance to achieve CR. In our analysis the most profound advantage was found in a cohort of 'young adults' i.e. patients aged 21–40 years with significant improvement for all the OS, LFS and RD. It must be stressed, however, that other age intervals, in particular 'adolescents', and 'elderly patients' were represented by relatively small numbers of observations. On the other hand it may be hypothesised that 'young adults' are the group with relatively high potential to be cured if adequate intensity of chemotherapy regimens is maintained.

G-CSF may be administered in different modes i.e. concurrently with chemotherapy, in an intermittent way or after completion of anthracycline-containing phase of the regimen. Initial reports indicate all modes to be safe. Individual decisions should probably take into account type of the chemotherapy protocol and possibly economical aspects.

In conclusion, the prophylactic use of G-CSF during induction is associated with improved laeukemia-free survival and prolonged remission duration in adults and adolescents with ALL and should be considered a standard of care. Our analysis provides the first direct evidence coming from prospective trials for the impact of primary G-CSF prophylaxis on disease-free survival of oncological patients.

Conflict of interest statement

Sebastian Giebel received honoraria for Amgen. Klaus Geissler has advisory relationships and received honoraria form Amgen and Ratiopharma. Urlich Jaeger has advisory relationships and received honoraria form Amgen and Ratiopharma, received research funding from Amgen. Remaining authors do not have any conflict of interest to be disclosed.

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