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Results of successive EORTC-CLG 58 881 and 58 951 trials in paediatric T-cell acute lymphoblastic leukaemia (ALL)

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Summary

Outcomes in childhood T-cell acute lymphoblastic leukaemia (T-ALL) are steadily improving due to intensive therapy. Between 1989 and 2008, 599 children with newly diagnosed T-ALL were enrolled in two successive European Organization for Research and Treatment of Cancer - Children's Leukaemia Group trials (58881 and 58951), both based on the Berlin-Frankfurt-Munster protocol and without cranial irradiation. In the latter trial induction chemotherapy was intensified. The most important randomizations were Medac *Escherichia coli* asparaginase *versus Erwinia* asparaginase in trial 58881, and dexamethasone (6 mg/m^2/day) *versus* prednisolone (60 mg/m^2/day) and prolonged *versus* conventional asparaginase duration in trial 58951. 8-year event-free survival (EFS) increased from 65·1% to 74·0% in trial 58951. Improvement was most profound for patients with white blood cell (WBC) counts <100 × 10^9/l and "good responders" to prephase. Medac *E. coli* asparaginase was associated with longer EFS [hazard ratio (HR) 0·54, P = 0·0015] and overall survival (HR 0·51, P = 0·0018). Induction therapy with dexamethasone did not improve EFS compared to prednisolone. Remarkably, intensification of central nervous system (CNS)-directed therapy in trial 58951 resulted in fewer bone marrow relapses, while the incidence of CNS relapses remained low. In summary, we showed that adequate asparaginase therapy, intensified induction treatment and intensification of CNS-directed chemotherapy can result in an improvement of outcome in T-ALL patients with good prephase response and initial WBC counts <100 × 10^9/l, representing approximately 50% of T-ALL patients.

Keywords: T-cell acute lymphoblastic leukaemia, EORTC, childhood leukaemia, asparaginase, cranial radiotherapy.

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Highlights

- Medac *E. coli* asparaginase is superior to non-Medac asparaginase in paediatric T-ALL.
- There is no evidence for prolonged asparaginase treatment benefit in T-ALL patients.
- Dexamethasone induction in a dose of 6 mg/m^2/day is not superior to prednisolone 60 mg/m^2/day.
- The long-term efficacy of a frontline treatment strategy without cranial radiotherapy is demonstrated.
- Post-induction MRD $\geq 10^{-2}$ is associated with worse EFS and OS, despite treatment intensification.

Childhood T-cell acute lymphoblastic leukaemia (ALL) accounts for approximately 12–15% of newly diagnosed ALL cases. Due to intensive therapy, outcomes in T-ALL are steadily improving with the 5-year event-free survival (EFS) rate increasing from 60% in the mid-nineties to more than 80% in contemporary clinical trials (Moricke *et al*, 2010, 2016; Hunger *et al*, 2012; Matloub *et al*, 2016; Raetz & Teachey, 2016). Despite advances in therapy, childhood T-ALL still has an inferior prognosis compared to B-cell precursor ALL (B-ALL). In particular, early disease recurrence with poor response to salvage therapy and treatment-related late effects remain important challenges (Reismuller *et al*, 2009, 2013).

Identification of high-risk T-ALL patients based on biological characteristics [white blood cell (WBC) count at diagnosis, central nervous system (CNS)-positivity] and treatment response, has led to treatment intensification in current protocols. Currently, the most important independent prognostic determinant in T-ALL is minimal residual disease (MRD) response at the end of induction and at the end of the consolidation phase. Nevertheless, the majority of relapses occurs in patients with favourable MRD status (Schrappe *et al*, 2011). Unlike in B-ALL, presence of recurrent chromosomal

translocations does not independently predict outcome (van Grotel *et al*, 2006, 2008) and hence, they are not included in patient stratification strategies. In contrast, next-generation sequencing (NGS) has recently revealed the prognostic impact of several oncogenetic mutational profiles (Petit *et al*, 2018).

Compared to children with B-ALL, T-ALL patients are at higher risk for CNS relapse and therefore adequate prophylaxis and/or treatment of CNS involvement is essential. CNS treatment includes cranial or craniospinal radiotherapy (CRT), intrathecal (IT) therapy and systemic chemotherapy (Richards *et al*, 2013). CRT has several undesirable late effects, such as endocrine abnormalities, cognitive impairment and secondary malignancies. This led the use of CRT to be questioned in all paediatric ALL and non-Hodgkin lymphoma (NHL) patients (Follin & Erfurth, 2016; Follin *et al*, 2016; Taskinen *et al*, 2017). The European Organization for Research and Treatment of Cancer - Children's Leukaemia Group (EORTC-CLG) 58832 trial was the first to address the question of whether CRT may be removed from ALL treatment in a randomized manner (Vilmer *et al*, 2000). Medium- and high-risk B- and T-patients, without initial CNS involvement and in complete remission (CR) after consolidation, received high dose methotrexate (HD MTX) intravenously (IV) and seven IT MTX injections during late intensification and were subsequently randomized to receive or not prophylactic CRT before the start of maintenance therapy. Substitution of CRT by HD MTX alone yielded not inferior disease-free survival and CNS relapse incidences. Consequently, CNS-directed chemotherapy replaced CRT in the following EORTC-CLG 58881 trial (Vilmer *et al*, 2000). The latter trial demonstrated that intensification of CNS-directed chemotherapy, without CRT, is an effective treatment of initial meningeal leukaemic involvement and that CNS-directed chemotherapy was not associated with an increase in isolated CNS relapse rates (Sirvent *et al*, 2011).

Interestingly, a meta-analysis on the use of CRT in children with ALL showed better outcome for children with T-ALL with slow early response in clinical trials without CRT (Vora *et al*, 2016). Nevertheless, the strength of this finding was limited by the low number of patients ($n = 133$) in this sub-analysis. Conversely, another meta-analysis, which specifically focused on T-ALL, found similar EFS with any of three approaches: CRT for all patients, CRT for CNS-positive patients or CRT omitted (Kelly *et al*, 2014). However, this meta-analysis was hampered by limited sample sizes in the included studies, so caution needs to be applied (Kelly *et al*, 2015). At present, the administration of CRT for T-ALL varies across international paediatric oncology groups, with some protocols including (low-dose) CRT for all patients and some including CRT for a subset of patients, while other protocols omit CRT entirely (Moghrabi *et al*, 2007; Kamps *et al*, 2010; Moricke *et al*, 2010; Pui *et al*, 2010; Schrappe *et al*, 2011; Mondelaers *et al*, 2017). In addition, no improved survival in children with B-ALL could be demonstrated with administration of CRT (Clarke *et al*, 2003; Richards *et al*, 2013; Vora *et al*, 2016).

We sought to evaluate the long-term outcomes of children with newly diagnosed T-ALL enrolled in two consecutive EORTC-CLG phase III trials (58881 and 58951), both of which used Berlin-Frankfurt-Munster (BFM)-based protocols, and without front-line cranial or local radiotherapy. Both trials investigated three questions in a randomized manner. These were, in trial 58881: (i) Medac *Escherichia coli* asparaginase *versus Erwinia* asparaginase (Duval *et al*, 2002), (ii) addition of high-dose IV cytarabine (HD IV Ara-C) during postinduction-consolidation therapy in increased-risk patients (Millot *et al*, 2001), and (iii) addition of monthly IV 6-mercaptopurine (IV 6-MP) to conventional continuation therapy (van der Werff Ten Bosch *et al*, 2005), and, in trial 58951: (i) dexamethasone *versus* prednisolone during induction and maintenance (Domenech *et al*, 2014), (ii) increasing the number of administrations of asparaginase during consolidation and late intensification (Mondelaers *et al*, 2017), (iii) vincristine + corticosteroid pulses or no pulses during continuation treatment (De Moerloose *et al*, 2010).

Methods

Patients

From 1989 to 1998 and from 1998 to 2008, children under 18 years of age with previously untreated ALL or lymphoblastic NHL were included in two successive EORTC-CLG trials, trial 58881 and 58951, respectively. In both trials, diagnosis of ALL was defined by the presence of more than 25% blasts in the bone marrow aspirate; T-cell lineage and T-ALL sub-classification was assessed by immunophenotyping according to the guidelines of the European Group for the Immunological Characterization of Leukaemias (EGIL) as previously described (Bene *et al*, 1995). All patients were stratified into different risk groups as described in the Data S1. T-ALL patients were either increased risk (IR) or very high risk (VHR) in protocol 58881, or average risk 2 (AR2) or VHR in protocol 58951. Informed consent from the parents or the legal guardian was provided before entry in the study according to the Declaration of Helsinki. The protocols were approved by the EORTC Protocol Review Committee and by the local institutional ethical committees in each participating centre.

Treatment

The treatment regimen of the 58881 trial was adapted from the BFM protocol, as previously described (Vilmer *et al*, 2000). Main modifications introduced in the 58951 trial for treatment of T-ALL patients were the administration of an intensified induction protocol with cyclophosphamide

1 g/m^2 and the first HD MTX course (5 g/m^2) administered at the start of induction. Noteworthy in this trial, all patients were randomized on day 1 or day 8 of the prephase to receive either prednisolone (60 mg/m^2/day) or dexamethasone (6 mg/m^2/day) during induction (Domenech *et al*, 2014). In trial 58951, MRD monitoring was performed on day 35 and was based on quantitative detection of leukaemic clone-specific T-cell-receptor gene rearrangements as previously described and was considered positive if $\geq 10^{-2}$ (Cave *et al*, 1994; Guidal *et al*, 2002).

The CNS-directed therapy consisted only of chemotherapy as CRT was omitted in both trials (Figure S1). The main difference between CNS-directed therapies in both trials was the type and number of IT injections. In trial 58881, IR and VHR patients received at least 4 HD MTX courses and received, respectively, 10 and 16 IT MTX injections, of which 6 were a combination of MTX, Ara-C and hydrocortisone (triple IT) in VHR patients. In trial 58951, IT therapy consisted of MTX only on day 1 and triple IT further on. AR2 and VHR patients received, respectively, a total of 16 and 20 IT injections and 11 and 10 HD MTX courses. Patients with T-ALL and poor response to prephase or high levels of MRD after induction ($\geq 10^{-2}$) were eligible for haematopoietic stem cell transplantation.

Definitions and evaluations

Definitions of complete remission and CNS disease have been published previously (De Moerloose *et al*, 2010; Domenech *et al*, 2014) and are summarized in the Data S1.

Statistics

The primary endpoints of both trials were EFS and disease-free survival (DFS). Secondary endpoint was overall survival (OS). Information on endpoint definitions, randomization technique, stratification factors and statistical analysis is included in the Data S1.

Results

Patient characteristics

Between 1989 and 2008, 599 children with newly diagnosed T-ALL were enrolled in EORTC-CLG trials 58881 (303 patients) and 58951 (296 patients), representing 14·5% and 15·2% of all enrolled ALL patients in these trials. Detailed patients' characteristics are shown in Table I. The male/female ratio of the T-ALL subgroup was 2·9 and 2·4 respectively and the median age at registration was 7 and 8 years, respectively. The median WBC count was 91·7 and 55·0 $\times$ 10^9/l and 46·2% and 36·5% of the patients had a WBC count $\geq$100 $\times$ 10^9/l, respectively.

At the end of prephase, 61·1% of patients were classified as "good responders" in trial 58881 and 64·9% in trial 58951. CR after first induction was observed in 89% and 95% patients, respectively. MRD was evaluated only in trial 58951, at day 35, and was positive in 36 patients (MRD level $\geq 10^{-2}$) of which 26 showed a good prephase response (GPR). The median follow-up in trial 58881 was 7·2 vs. 6·8 years for trial 58951.

General outcome comparison between trial 58881 and 58951 for T-ALL patients

The outcome of T-ALL patients improved markedly from trial 58881 to trial 58951. The 8-year EFS improved from 65·1% to 74·0%, the 8-year DFS increased from 67·3% to 75·8% and the OS improved from 71·9% to 78·2% (Table II). Relapse rates were lower in the latter trial (58951), at 26·7% vs. 34·2% in trial 58881. The non-CNS 8-year cumulative incidence of relapse decreased from 16·5% in trial 58881 to 12·9% in trial 58951, whereas the 8-year isolated CNS relapse incidences were similar (6·8% vs. 5·3%), as were the 8-year overall CNS-positive relapse incidences (10·9% vs. 8·5%).

To explore which treatment component had most impact on the outcome of T-ALL patients, all randomized treatment comparisons in both trials were specifically checked for the T-ALL subgroup (Tables III and IV).

Subanalysis of trial 58881

Medac Escherichia coli *asparaginase* versus *Non-Medac asparaginase.* In protocol 58881, a first randomization compared the value of Medac *E. coli* asparaginase with *Erwinia* asparaginase, both administered IV twice weekly for a total of 12 doses of 10 000 international units (iu) each. However, before the randomization period started, some patients were treated with Bayer *E. coli* asparaginase, and after the end of the randomization period most patients received Medac *E. coli* asparaginase, and only a few received *Erwinia* asparaginase, hence, finally, we compared the outcomes of the Medac *E. coli* asparaginase group (n = 209) *versus* Non-Medac asparaginase group (n = 94). Outcomes were significantly better in the Medac *E. coli* asparaginase group: 8-year EFS rate was 71·6% vs. 52·1% in the Non-Medac asparaginase treated group [hazard ratio (HR) 0·54, 99% confidence interval (CI) 0·32–0·90, P = 0·0015], and 8-year OS rate was 77·7% vs. 59·6% (HR 0·51, 99% CI 0·29–0·90, P = 0·0018) (Figure S2). Complete remission rates were similar (97·6% vs. 94·7%). The relapse rate for the Medac *E. coli* asparaginase group was lower than in the Non-Medac group (22·5% vs. 38·2%), as the isolated CNS relapse rate (5·4% vs. 10·1%) and any CNS relapse rate was lower (18% vs. 8·4%), as was the isolated + combined bone marrow relapse rate (13·8% vs. 19·1%).

Exploratory subgroup analyses indicated that older T-ALL patients (≥10 years old) in particular, and children with VHR features exhibited shorter EFS in the Non-Medac asparaginase group.

Table I. Distribution of patient characteristics and treatment groups in EORTC-CLG trials 58 881 and 58 951

	Trial 58881	Trial 58951
Total number of patients	2065	2038
Number of T-ALL patients	303	296
% of total ALL population	303/2065 (14·5%)	296/2038 (15·2%)
Median follow-up (95% CI) (years)	7·16 (6·57–7·58)	6·82 (6·07–7·35)
Gender		
Male	225 (74·3%)	209 (70·6%)
Female	78 (25·7%)	87 (29·4%)
Age (years)		
Median	7·0	8·0
Range	0–17	0–17
WBC count ($\times 10^9$/l)		
Median	91·7	55
Range	0·3–988·0	0·2–1000·0
WBC count $\geq 100 \times 10^9$/l	140 (46·2%)	108 (36·5%)
Mediastinal involvement	188 (62·0%)	138 (46·6%)
Gonadal involvement	7 (2·3%)	2 (0·7%)
CNS-3	22 (7·3%)	20 (6·8%)
Prephase response		
Good ("GPR")	185 (61·1%)	192 (64·9%)
Poor ("PPR")	117 (38·6%)	102 (34·5%)
VHR		
After prephase	118 (38·9%)	106 (35·8%)
After induction	126 (41·6%)	109 (36·8%)
Complete response		
At any point during therapy	293 (96·7%)	281 (94·9%)
Treatment group step 1		
Medac *Escherichia coli* asparaginase	209	
Non-Medac asparaginase	94	
Randomized question 2		
Cytarabine	46 (15·2%)	
No cytarabine	34 (11·2%)	
Randomized question 3		
IV mercaptopurine	53 (17·5%)	
PO mercaptopurine	50 (16·8%)	
Randomized question 1		
Dexamethasone induction		145 (49·0%)
Prednisolone induction		151 (51·0%)
Randomized question 2		
Long asparaginase		73 (24·7%)
Short asparaginase		74 (25·0%)
Randomized question 3		
Corticosteroid pulses		22 (7·4%)
No corticosteroid pulses		23 (7·8%)

ALL, acute lymphoblastic leukaemia; CI, confidence interval; CNS-3, central nervous system stage 3; EORTC-CLG, European Organization for Research and Treatment of Cancer-Children's Leukaemia Group; GPR, good prephase response; IV, intravenously; PO, orally; PPR, poor prephase response; T-ALL, T-cell acute lymphoblastic leukaemia; VHR, very high risk; WBC, white blood cell.

No impact of high dose cytarabine during interval therapy. In trial 58881, 653 IR ALL children were randomized to receive or not HD IV Ara-C during interval therapy. The addition of HD IV Ara-C to HD MTX failed to decrease the incidence of CNS relapse or prolong DFS (HR: 1·06) (Millot *et al*, 2001). Similar findings were observed when the treatment comparison was restricted to T-ALL patients ($n = 80$): 8-year DFS rate was 67·4% (with HD IV Ara-C) vs. 73·5% (without HD IV Ara-C).

Monthly intravenous mercaptopurine during maintenance was associated with worse EFS. The last question of the 58881 trial evaluated the monthly addition of IV 6-MP to conventional continuation therapy (van der Werff Ten Bosch *et al*,

Table II. General outcome results in T-ALL patients

	Trial 58881 (n = 303) (SE)	Trial 58951 (n = 296) (SE)
8-year OS	71·9% (2·6%)	78·2% (2·5%)
8-year EFS	65·1% (2·6%)	74·0% (2·6%)
8-year DFS	67·3% (2·8%)	75·8% (2·6%)
No CR reached	3·3%	3·3%
8-year cumulative incidence by event		
Isolated CNS	6·8%	5·3%
Any CNS	10·9%	8·5%
Non-CNS	16·5%	12·9%
Death in CR	5·3%	2·9%

CNS, central nervous system; CR, complete remission; DFS, disease-free survival; EFS, event-free survival; OS, overall survival; SE, standard error; T-ALL, T-cell acute lymphoblastic leukaemia.

2005). A total of 103 T-ALL patients were randomized for this question. Both DFS and OS were significantly lower in the IV 6-MP arm (64·2% and 69·8%, respectively) compared to control arm (79·4% and 88%, respectively).

Sub-analysis of trial 58951

Dexamethasone versus *Prednisolone in induction treatment: no difference in outcome.* In trial 58951, 135 patients were randomized to receive dexamethasone and 145 prednisolone during induction treatment. At a median follow-up of 6·8 years, 42 events were reported in the dexamethasone group and 35 in the prednisolone group. No significant differences in 8-year EFS and OS rates could be observed. Distribution of the type of relapses were similar in the two treatment groups, and subgroup exploratory analyses according to initial WBC count, age, risk group or response to prephase indicated consistent findings.

No evidence for prolonged asparaginase treatment nor pulsed therapy. The second randomization evaluated, in average risk patients, the value of prolonged *versus* standard native *E. coli* asparaginase treatment during consolidation and late intensification. A total of 147 T-ALL children were randomized. The 8-year DFS rate was 82·9% in the prolonged asparaginase arm and 82·1% in the standard arm (HR: 0·94, P = 0·88). Relapse rates were comparable for both arms (16·4% vs. 17·6%), as was the distribution of type of relapses.

Finally, trial 58951 also addressed the benefit of corticosteroid pulses during continuation treatment. Only 45 T-ALL patients were randomized. Therefore, no strong conclusions can be drawn from the present results (8-year DFS rate: 95·5% vs. 91·3% and 8-year OS rate: 95·5% vs. 95·6%).

Minimal residual disease was a strong prognostic factor. In trial 58951, MRD was assessed at day 35 on 227 of 281 patients who reached CR: 36 had MRD $\geq 10^{-2}$ and 191 had MRD $< 10^{-2}$. In the first group, despite a switch to a more intensive treatment, the 8-year EFS rate was 49·5%, far lower than the 79·3% observed in the latter group, and the 8-year OS rate was 49·5% vs. 85·6%. Of 77 patients with poor prephase response (PPR), those with MRD $\geq 10^{-2}$ (n = 25) had an 8-year EFS rate of 38·8%, whereas it was 73·0% for those with MRD $< 10^{-2}$ (n = 52).

Impact of CNS-directed treatment

In both trials, a group of patients (209 patients in trial 58881 and 151 in trial 58951) were treated with prednisolone induction, Medac *E. coli* asparaginase and a similar BFM backbone. The main differences in treatment between these patient groups were the use of an intensified induction scheme (with cyclophosphamide 1 g/m^2 and HD MTX 5 g/m^2 at the beginning of phase 1A) and intensification of CNS-directed chemotherapy in trial 58951. In this patient subgroup, a moderate outcome improvement could be observed between both successive trials (8-year EFS: 71·6% vs. 76·7%) (Table V). Intensification of CNS-directed chemotherapy in trial 58951 did not reduce the isolated or total CNS relapse rates (5·4% and 8·4% vs. 5·5% and 9·8%) as compared to the 58881 trial. Interestingly, a decrease in non-CNS relapses was observed (14·4% vs. 10·5%) in trial 58951, together with a lower risk of death in complete remission (3·9% vs. 1·5%).

In patients with GPR (n = 225), intensification of CNS-directed chemotherapy resulted in an outcome improvement. This was marked in patients with a WBC $< 100 \times 10^9$/l (n = 157): in trial 58881 (n = 85), the 8-year EFS and 8-year OS rates were 75·3% and 82·1%, respectively, whereas in trial 58951 (n = 72), the respective rates were 84·6% and 93·0% (Fig 1). In the subgroup of patients with GPR and WBC $\geq 100 \times 10^9$/l (n = 68) or in those with a PPR (n = 130), the outcomes did not improve.

Discussion

The outcome of children with T-ALL improved markedly between the successive EORTC-CLG 58881 and 58951 trials, with 8-year OS reaching almost 80% in the latter trial. These results are in line with long-term outcome results reached in other trials performed in the same era (Fig 2) (Kamps *et al*, 2002, 2010; Moghrabi *et al*, 2007; Ballerini *et al*, 2008; Moricke *et al*, 2008, 2010, 2016; Conter *et al*, 2010; Pui *et al*, 2010; Salzer *et al*, 2010; Schmiegelow *et al*, 2010; Silverman *et al*, 2010; Tsuchida *et al*, 2010; Hunger *et al*, 2012; Petit *et al*, 2018). The first randomization of trial 58881 showed that some of this improvement can be attributed to adequate asparaginase treatment with *E. coli* asparaginase. Adequate asparaginase treatment also resulted in similar outcome improvements in patients with B-ALL and NHL (Duval *et al*, 2002). Importantly, trial 58951 showed that prolongation of native *E. coli* asparaginase therapy in consolidation and late intensification did not result

Table III. Comparison of the outcomes in EORTC-CLG trial 58881 on paediatric T-ALL

Treatment group step 1	Medac *Escherichia coli* asparaginase (n = 209)	Non-Medac asparaginase (n = 94)	Hazard ratio (99% CI) for Medac *E. coli* asparaginase *versus* non-Medac asparaginase	P-value
8-year EFS	71·6% (SE: 3·1)	52·1% (SE: 5·2)	0·54 (0·32–0·90)	0·0015
8-year DFS	73·3% (SE: 3·1)	55·0% (SE: 5·3)	0·55 (0·37–0·83)	0·0036
8-year OS	77·7% (SE: 3·0)	59·6% (SE: 5·1)	0·51 (0·29–0·90)	0·002
CR reached during therapy	204 (97·6%)	89 (94·7%)		
Relapse	46 (22·5%)	34 (38·2%)		
Isolated CNS	11 (5·4%)	9 (10·1%)		
Any CNS	17 (8·4%)	16 (18%)		
Isolated BM	23 (11·3%)	13 (14·6%)		
Any BM	28 (13·8%)	17 (19·1%)		
Other sites	1 (0·5%)	1 (1·1%)		
Death in CR	8 (3·9%)	7 (7·9%)		

Randomization 2	With Ara-C during interval therapy (n = 46)	Without Ara-C during interval therapy (n = 34)	Hazard ratio (99% CI) for Ara-C *versus* no Ara-C	
8-year DFS	67·4% (SE: 6·9)	73·5% (SE: 7·6)	1·35 (0·46–3·95)	0·47
8-year OS	76·1% (SE: 6·3)	76·5% (SE: 7·3)	1·04 (0·31–3·43)	0·94
Relapse	13 (28%)	8 (23·5%)		

Randomization 3	Mercaptopurine IV during maintenance (n = 53)	Mercaptopurine PO during maintenance (n = 50)	Hazard ratio (99% CI) for mercaptopurine IV *versus* mercaptopurine PO	
8-year DFS	64·2% (SE: 6·6)	79·4% (SE: 5·8)	2·15 (0·79–5·84)	0·044
8-year OS	69·8% (SE: 6·3)	88% (SE: 4·6)	2·87 (0·83–9·84)	0·021
Relapse	17 (32·1%)	10 (20%)		

Ara-C, cytarabine; BM, bone marrow; CI, confidence interval; CNS, central nervous system; CR, complete remission; DFS, disease-free survival; EFS, event-free survival; EORTC-CLG, European Organization for Research and Treatment of Cancer-Children's Leukaemia Group; IV, intravenously; OS, overall survival; PO, orally; SE, standard error; T-ALL, T-cell acute lymphoblastic leukaemia.

in an additional gain in outcome. On the contrary, prolonged asparaginase treatment can lead to an increased risk of infections and allergy (Mondelaers *et al*, 2017).

Noteworthy, supportive care changes over time which may also impact outcome results of successive trials. However, regarding the EORTC-CLG trials in this study, there were no major changes in supportive care guidelines for the participating sites. To overcome bias introduced by differences in treatment we performed a direct comparison of patients treated with the same BFM backbone, prednisolone induction and *E. coli* asparaginase. This comparison showed an additional outcome improvement in the second trial, which presumably could be attributed to the adaptation of an intensified induction and CNS-directed treatment regimen (protocol with HD MTX and triple IT chemotherapy consisting of MTX, Ara-C and hydrocortisone). We demonstrated that patients with GPR and WBC count at diagnosis $<100 \times 10^9$/l in particular, benefited from this intensification with an increase in OS of more than 10%, thus reaching 93%. In contrast, in patients with PPR no outcome improvement was obtained, suggesting the need for other treatment options in these patients.

We demonstrate the long-term efficacy of a frontline treatment strategy without prophylactic and therapeutic CRT. No differences in isolated and combined CNS relapse rates were observed compared with other contemporary trials on T-ALL, independent of the type of CNS-directed therapy (Pui *et al*, 2009; Moricke *et al*, 2010; Vora *et al*, 2016). However, the limited number of studies on paediatric T-ALL patients must be taken into account. Remarkably, intensification of CNS-directed therapy in trial 58951 reduced the non-CNS related relapse rate (bone marrow and other sites), whereas only moderate improvement was seen on isolated or combined CNS relapse rates, indicating the systemic effect of intensification of CNS-directed therapy. This is in contrast to evidence from the Children's Oncology Group, who reported more bone marrow and testicular relapses with triple therapy compared to IT MTX alone (Matloub *et al*, 2006).

The *in vitro* cytotoxic effect of dexamethasone on lymphoblasts is stronger than that of prednisolone (Ito *et al*, 1996; Kaspers *et al*, 1996). Also, dexamethasone revealed greater CNS penetration, which is of interest in T-ALL, considering the higher rates of CNS disease and CNS relapses (Balis *et al*, 1987). Therefore, several study groups have supported and

Table IV. Impact of different randomization steps in EORTC-CLG trial 58951 on paediatric T-ALL

Randomization 1	Dexamethasone (n = 145)	Prednisolone (n = 151)	Hazard ratio (99% CI) for dexamethasone *versus* prednisolone	*P*-value
8-year EFS	71·3% (SE: 3·8)	76·7% (SE: 3·5)	1·26 (0·70–2·28)	0·31
8-year DFS	73·3% (SE: 3·8)	78·2% (SE: 3·5)	1·25 (0·78–2·00)	0·35
8-year OS	74·2% (SE: 3·8)	84·1% (SE: 3·2)	1·46 (0·76–2·80)	0·13
Relapse	32 (22·1%)	29 (19·2%)		
Isolated CNS	7 (4·8%)	8 (5·3%)		
Any CNS	10 (6·9%)	14 (9·2%)		
Isolated BM	19 (13·1%)	11 (7·3%)		
Any BM	23 (15·7%)	20 (13·2%)		
Other sites	2 (1·4%)	1 (0·7%)		
Death in CR	6 (4·1%)	3 (2%)		
Randomization 2	Prolonged asparaginase treatment (n = 73)	Short asparaginase treatment (n = 74)	Hazard ratio (99% CI) for prolonged asparaginase *versus* short asparaginase	
8-year DFS	82·9% (SE: 4·5)	82·1% (SE: 4·5)	0·94 (0·34–2·64)	0·88
8-year OS	87·4% (SE: 3·9)	91·9% (SE: 3·2)	1·35 (0·37–4·94)	0·55
Relapse	12 (16·4%)	13 (17·6%)		
Randomization 3	Corticosteroid pulses (n = 22)	No corticosteroid pulses (n = 23)		
8-year DFS	95·5% (SE: 4·4)	91·3% (SE: 5·9)	NA	NA
8-year OS	95·5% (SE: 4·4)	95·7% (SE: 4·3)	NA	NA
Relapse	1 (4·5%)	2 (8·7%)		

BM, bone marrow; CI, confidence interval; CNS, central nervous system; CR, complete remission; DFS, disease-free survival; EFS, event-free survival; EORTC-CLG, European Organization for Research and Treatment of Cancer-Children's Leukaemia Group; IV, intravenously; NA, not applicable (too few events reported) OS, overall survival; PO, orally; SE, standard error; T-ALL, T-cell acute lymphoblastic leukaemia.

Table V. Intensification of CNS-directed chemotherapy: comparison between patients treated with the same backbone (Medac *Escherichia coli* asparaginase and Prednisolone) in EORTC-CLG trial 58881 and 58951

	Trial 58881 (n = 209)	Trial 58951 (n = 151)
8-year EFS	71·6% (SE 3·1)	76·6% (SE 3·5)
8-year OS	77·7% (SE 3·0)	82·1% (SE 3·2)
8-year cumulative incidence by event		
Isolated CNS	5·4%	5·5%
Any CNS	8·4%	9·8%
Non-CNS	14·4%	10·5%
Death in CR	3·9%	1·5%
GPR	n = 126	n = 99
8-year EFS	76·7% (SE 3·8)	81·6% (SE 3·9)
8-year OS	84·7% (SE 3·2)	88·9% (SE 3·2)
WBC count $<100 \times 10^9$/l	n = 85	n = 72
8-year EFS	75·3% (SE 4·7)	84·6% (SE 4·3)
8-year OS	82·1% (SE 4·2)	93·0% (SE 3·1)
WBC count $\geq 100 \times 10^9$/l	n = 41	n = 27
8-year EFS	79·7% (SE 6·4)	73·6% (SE 8·6)
8-year OS	90·2% (SE 4·6)	78·0% (SE 7·9)
PPR	n = 82	n = 48
8-year EFS	64·5% (SE 5·3)	67·6% (SE 7·0)
8-year OS	67·5% (SE 5·7)	70·5% (SE 7·1)

CNS, central nervous system; CR, complete remission; EFS, event-free survival; EORTC-CLG, European Organization for Research and Treatment of Cancer-Children's Leukaemia Group; GPR, good prephase response; PPR, poor prephase response; SE, standard error; WBC, white blood cell.

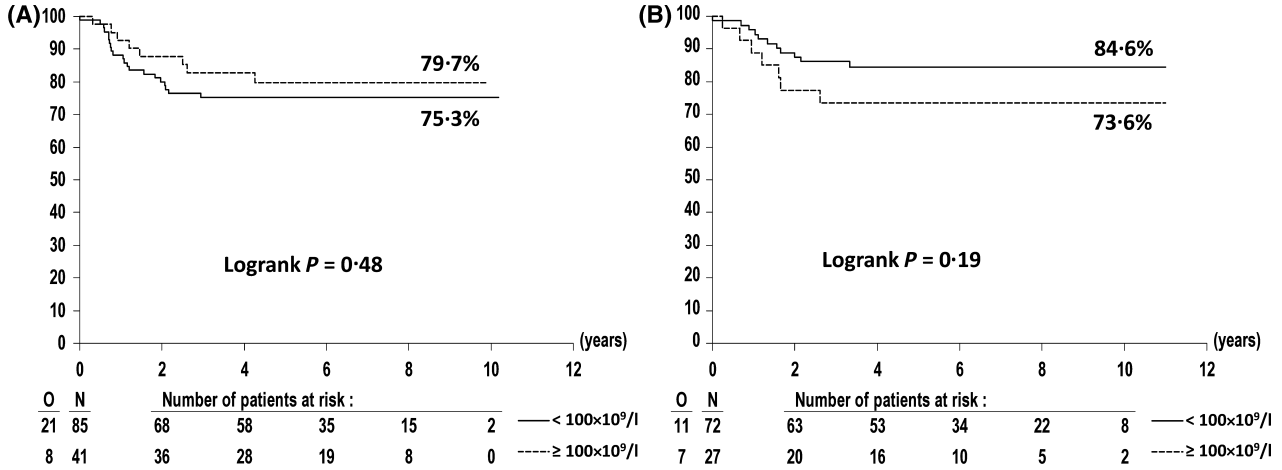

Fig 1. EFS according to WBC count at diagnosis in patients with a "good response to prephase", receiving similar background therapy in trial 58881 and 58951. Event-free survival (EFS) according to white blood cell (WBC) count at diagnosis (<100 × 10^9/l [continuous line] vs. ≥100 × 10^9/l [dashed line]) in (A) patients receiving Medac *Escherichia coli* asparaginase in trial 58881 and (B) patients randomized to prednisolone treatment in trial 58951. Both patient groups received a similar Berlin-Frankfurt-Munster-backbone, prednisolone induction and Medac *E. coli* asparaginase treatment. A marked outcome improvement could be seen in patients with a diagnostic WBC count <100 × 10^9/l. O, observed events; N, number.

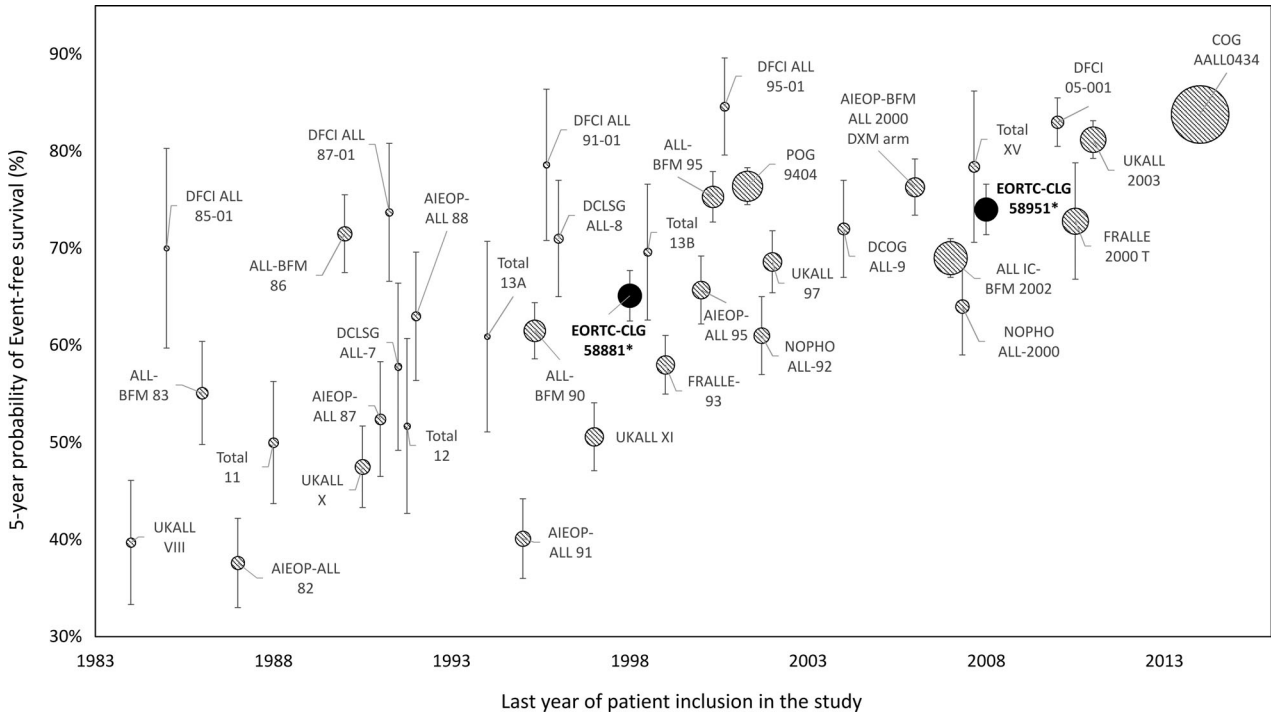

Fig 2. Qualitative impact of 'end year of study inclusion' on survival rates in children with T-ALL. Every study, depicted by a solid dot, is labelled with the study name. *x*-axes refers to 'the end year of study-inclusion' of each study, the *y*-axes illustrate the 5-year* probability of event-free survival. The standard error of each study is depicted and the size of the dot is a measure of the number of patients included in the study. Both EORTC-CLG trials are depicted with solid dots. *The 8-year EFS is shown For both EORTC-CLG trials (58881 and 58951). AIEOP, Associazione Italiana di Ematologia e Oncologia Pediatrica; ALL, acute lymphoblastic leukaemia; COG, Children's Oncology Group; DCLSG, Dutch Childhood Leukaemia Study Group; DCOG, Dutch Children's Oncology Group; DFCI, Dana Farber Cancer Institute; EORTC-CLG, European Organization for Research and Treatment of Cancer-Children's LeukaemiaGroup; FRALLE, French Acute Lymphoblastic Leukaemia Study Group; (IC)-BFM, (intensive chemotherapy) Berlin-Frankfurt-Munster; NOPHO, Nordic Society for Paediatric Haematology and Oncology; UKALL; United Kingdom acute lymphoblastic leukaemia.

incorporated the use of dexamethasone in paediatric T-ALL trials (Mitchell *et al*, 2005; Moricke *et al*, 2016). Surprisingly, our long-term outcome results show that dexamethasone (6 mg/m^2/day) is not superior to prednisolone induction (60 mg/m^2/day) in T-ALL patients, for both GPR and PPR patients. These data are in line with a review from Teuffel *et al* (2011), which could not demonstrate superior long-term OS with dexamethasone induction in ALL children. In contrast, the Associazione Italiana di Ematologia e Oncologia Pediatrica-BFM 2000 trial has shown that administration of a higher dose of dexamethasone (10 mg/m^2) in children with T-ALL and good early treatment response resulted in prolonged EFS and OS and in relapse reduction (Moricke *et al*, 2016).

Despite marked improvement of outcome in T-ALL patients over time, the prognosis is still worse compared to B-ALL. Early disease recurrence and low numbers of successful remission re-induction can account for these differences. Therefore, future efforts should focus on fast identification and treatment intensification for patients at higher risk for relapse, and discovery of novel therapies for relapsed patients. The AIEOP-BFM-ALL 2000 trial was the first to incorporate MRD based on immunoglobulin and T-cell receptor gene rearrangements as polymerase chain reaction targets for stratification. They showed that MRD negativity on day 33 was the most favourable prognostic factor, MRD positivity ($\geq 10^{-3}$) at day 78 the most important predictor for relapse, and that MRD also had an impact on the incidence of relapses with extramedullary components (Schrappe *et al*, 2011). In trial 58951, patients with MRD $\geq 10^{-2}$ were switched to the VHR group and received a more intensive treatment. Despite this, our results demonstrated that MRD levels $\geq 10^{-2}$ on day 35 are associated with worse EFS and OS. In another trial, we showed that NOTCH pathway activation (due to *NOTCH1* and *FBXW7* mutations) was associated with favourable early treatment response (Clappier *et al*, 2010). In this respect, Petit *et al* (2018) revealed that MRD in combination with oncogenetic mutations can identify T-ALL patients with worse prognosis. Therefore, incorporation of these prognostic features in future trials and adaptation of therapy is warranted.

In summary, we showed that adequate asparaginase (and not prolonged) therapy during induction, intensified induction treatment and intensification of CNS-directed chemotherapy can improve the outcome in patients with GPR and initial WBC counts $<100 \times 10^9$/l, representing approximately 50% of T-ALL patients. Also, we demonstrated that dexamethasone in a lower dose of 6 mg/m^2/day is not superior to prednisolone induction.

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Author contributions

Contribution: M.H. and B.D.M. checked the results and wrote the manuscript. S.S. (study statistician) analysed the data, designed the figures and tables and wrote the manuscript. Y.B and P.R. (previous and present chairmen, respectively, of the EORTC-CLG); planned and coordinated the study. A.F., F.M., N.S., V.C., K.Y., C.P., A.U., D.P., G.P., P.S., F.M., M.P., JvdWTB, C.P., O.M., P.R., S.G., H.C., Y.B. and B.D.M., included patients in the trial and provided clinical data. P.V.V. performed molecular analysis and carefully reviewed this paper. All authors participated in study supervision, data interpretation and critically reviewed the manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1.

Participating institutions and investigators/biologists of the EORTC-CLG to this study.

Figure S1. Detailed CNS directed therapy in EORTC-CLG trials 58881 and 58951.

Figure S2. EFS and OS for treatment with Medac *E. coli* asparaginase vs. non-Medac asparaginase for T-ALL patients included in trial 58881.

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