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REVIEW

The evolution of clinical trials for infant acute lymphoblastic leukemia

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Acute lymphoblastic leukemia (ALL) in infants has a significantly inferior outcome in comparison with older children. Despite initial improvements in survival of infants with ALL since establishment of the first pediatric cooperative group ALL trials, the poor outcome has plateaued in recent years. Historically, infants were treated on risk-adapted childhood ALL protocols. These studies were pivotal in identifying the need for infant-specific protocols, delineating prognostic categories and the requirement for a more unified approach between study groups to overcome limitations in accrual because of low incidence. This subsequently led to the development of collaborative infant-specific studies. Landmark outcomes have included the elimination of cranial radiotherapy following the discovery of intrathecal and high-dose systemic therapy as a superior and effective treatment strategy for central nervous system disease prophylaxis, with improved neurodevelopmental outcome. Universal prospective identification of independent adverse prognostic factors, including presence of a *mixed lineage leukemia* rearrangement and young age, has established the basis for risk stratification within current trials. The infant-specific trials have defined limits to which conventional chemotherapeutic agents can be intensified to optimize the balance between treatment efficacy and toxicity. Despite variations in therapeutic intensity, there has been no recent improvement in survival due to the equilibrium between relapse and toxicity. Ultimately, to improve the outcome for infants with ALL, key areas still to be addressed include identification and adaptation of novel prognostic markers and innovative therapies, establishing the role of hematopoietic stem cell transplantation in first complete remission, treatment strategies for relapsed/refractory disease and monitoring and timely intervention of late effects in survivors. This would be best achieved through a single unified international trial.

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INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common malignancy occurring in children and adolescents, accounting for ~20% of cancers in patients younger than 20 years of age.[1,2] Remarkable therapeutic advances have been made since Sidney Farber first reported temporary remission in five children with acute leukemia using the folate antagonist, aminopterin, in 1948.[3] The 5-year overall survival (OS) now exceeds 90%, with significant improvements in survival for subgroups according to age, sex, race, immunophenotype and National Cancer Institute risk status.[4] However, infants less than 1 year of age at diagnosis are the exception to this success. The initial modest improvement in survival following inception of cooperative group clinical trials has stalled with minimal gains over the past decade.[4] This review encompasses the evolution of clinical trials for infant ALL, from the risk-adapted protocols of the past to the current collaborative infant-specific studies, and provides perspectives for improving outcome for infant ALL in the future.

THE PAST: RISK-ADAPTED THERAPY ON CHILDHOOD LEUKEMIA STUDIES

The first cooperative clinical trials for childhood leukemia were established in the 1950s.[5] Initially all children were treated uniformly; however, it was soon recognized that certain clinical features at diagnosis had profound prognostic significance. The unfavorable prognosis carried by infants less than 1 year of age was identified following analysis of prognostic features from successive trials and registry data.[6–8] This led to the strategy of risk adaptation within clinical trials, with the majority increasing the intensity of therapy delivered to infants by stratification to high-risk arms. Table 1 summarizes published outcomes for infants treated within childhood ALL studies. Although the number enrolled onto each study was limited by the rarity of infant ALL, and several studies did not differentiate infants by B or T-cell lineage, they were fundamental in demonstrating the poor event-free survival (EFS) and OS of infants within high-risk strata of childhood ALL studies.

Combined analysis of infants treated on successive childhood ALL protocols within individual study groups identified key biological and clinical prognostic features. Presence of a *mixed lineage leukemia* (*MLL*) rearrangement,[9] hyperleukocytosis at presentation,[10] absence of CD10 antigen,[10] age <6 months at diagnosis[11] and poor response to initial prednisone therapy[11] were independently associated with an inferior outcome.

Despite suboptimal outcomes, this period in the history of clinical trials for infant ALL was pivotal in defining the foundations for future therapy, namely the need for infant-specific ALL protocols, delineation of prognostic categories to allow for risk stratification within infant ALL and a more unified approach between study groups to overcome limitations in accrual because of low incidence.

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Table 1. Summary of results for infants treated on childhood ALL protocols

Group *Country*	*Study*	*Year*	*Number of infants*	*5-Year EFS (%)*	*5-Year OS (%)*	*Reference*
AIEOP Italy	AIEOP-ALL 82 AIEOP-ALL 88 AIEOP-ALL 91 AIEOP-ALL 95	1982–1987 1988–1992 1991–1995 1995–2000	16 16 21 31	31.3 31.3 33.3 51.6	37.5 56.3 52.4 57.6	88
BFM Germany, Austria, Switzerland	ALL-BFM 81 ALL-BFM 83 ALL-BFM 86 ALL-BFM 90 ALL-BFM 95	1981–1983 1983–1986 1986–1990 1990–1995 1995–2000	9 13 34 60 33	55.6 23.1 38.2 51.6 38.5	100 46.2 50.0 58.3 44.7	89
CCG USA	CCG-192P	1982–1984	27	36.0[a]	—	13
EORTC-CLG France, Belgium, Portugal	58831 58832 58881	1983–1989 1989–1998	23 60	39[b] 42.5	— —	90
CoALL Germany	COALL 82 COALL 85 COALL 89 COALL 92	1982–1985 1985–1989 1989–1992 1992–1997	3 6 10 17	0.0 0.0 40.0 44.0	— — — —	91
CPH Czech Republic	ALL-BFM 83 ALL-BFM 90	1986–1990 1990–1996	14 13	— 30.8	— 30.8	92 93
DCOG The Netherlands	DCLSG-ALL-7 DCLSG-ALL-8	1988–1991 1991–1997	3 13	66.7 0.0	33.3 15.4	94
DFCI Dana-Farber Cancer Institute, USA	85-01 87-01 91-01 95-01	1985–1987 1987–1991 1991–1995 1996–2000	10 8 7 14	60.0 50.0 71.4 41.7	60.0 62.5 71.4 41.7	95
FRALLE France	FRALLE 83 FRALLE 87 FRALLE 89 FRALLE 93	1983–1986 1987–1989 1989–1992 1993–1999	 38 34	 — —	 — —	 96 97
INS Israel	ALL-INS 89 ALL-INS 98	1989–1997 1998–2003	10 12	50.0[b] 50.0[b]	60.0[b] 58.3[b]	98
JACLS Japan	No uniform study. Retrospective analysis of infants treated by JACLS institutions.	1991–1995	19	28.7[c]	—	99
JCCLSG Japan	ALL811 ALL841	1981–1984 1984–1987	9 7	33.3 57.1	44.4 71.4	100
KYCCSG Japan	AL851 ALHR88	1985–1988 1988–1990	7	—	—	101
Ma-Spore Malaysia, Singapore	Ma-Spore ALL 2003	2002–2011	21	52.4	—	102
NOPHO Denmark, Finland, Iceland, Norway, Sweden	No uniform study. Retrospective analysis of infants treated by NOPHO institutions	1981–1986 1986–1991 1992–1998	23 27 36	39.1 18.5 39.9	— — —	103
PETHEMA Spain	PETHEMA ALL-93	1993–2002	12	50.0[d]	—	104
PINDA Chile	PINDA 87	1987–1992	15	21	—	105
POG USA	POG 8398	1984–1990	33	17.7	36.4	19
SJCRH St Jude Children's Research Hospital, USA	Total Therapy Study 10 Total Therapy Study 11 Total Therapy Study 12 Total Therapy Study 13A Total Therapy Study 13B	1979–1983 1984–1988 1988–1991 1991–1994 1994–1998	5 11 8 5 10	20[e] 45.5 25.0 20.0 70.0	— 63.6 50.0 40.0 70.0	106 107

Table 1. (Continued)

Group Country	Study	Year	Number of infants	5-Year EFS (%)	5-Year OS (%)	Reference
TCCSG Japan	No uniform study. Retrospective analysis of infants treated by TCCSG institutions.	1977–1995	62	13.1	13.1	108
TPOG Taiwan	TPOG-ALL 97 TPOG-ALL 2002	1997–2001 2002–2007	19 32	55.3 32.0	56.3 30.4	109
UK CLWP UK	UKALL VIII UKALL X	1980–1984 1985–1990	20 26	30.0 26.9	— —	110

Abbreviations: AIEOP, Associazione Italiana Ematologia Oncologia Pediatrica; ALL, acute lymphoblastic leukemia; BFM, Berlin–Frankfurt–Münster study group; CCG, Children's Cancer Group; CoALL, Co-operative study group for treatment of ALL; CPH, Czech Pediatric Hematology working group; DCOG, Dutch Childhood Oncology Group; DFCI, Dana-Faber Cancer Institute consortium; EFS, event-free survival; EORTC-CLG, European Organization for Research and Treatment of Cancer–Children's Leukemia Group; FRALLE, French Acute Lymphoblastic Leukemia group; INS, Israeli National Studies of childhood ALL; JACLS, Japan Association of Childhood Leukemia Study; JCCLSG, Japanese Children's Cancer and Leukemia Study Group; KYCCSG, Kyushu Yamaguchi Children's Cancer Study Group; NOPHO, Nordic Society of Pediatric Hematology and Oncology; OS, overall survival; PETHEMA, Programa de Estudio Tratamiento de las Hemopatías Malignas; PINDA, Programa Infantil Nacional de Drogas Antineoplásicas; POG, Pediatric Oncology Group; SJCRH, St Jude Children's Research Hospital; TCCSG, Tokyo Children's Cancer Study Group; TPOG, Taiwan Pediatric Oncology Group; UK CLWP, United Kingdom Childhood Leukemia Working Party. [a]4-year EFS. [b]10-year EFS and OS. [c]3-year EFS. [d]5-year disease-free survival. [e]9-year EFS.

THE PRESENT: INFANT-SPECIFIC COLLABORATIVE GROUP PROTOCOLS

Currently, there are three large collaborative groups conducting infant ALL-specific clinical trials—the Children's Oncology Group (COG), the Japanese Pediatric Leukemia/Lymphoma Study Group (JPLSG) and the Interfant Study Group. Their trials and outcomes are described below and summarized in Figure 1 and Table 2.

Children's Oncology Group

Several US pediatric cooperative trial groups merged in the year 2000 to form the COG. Those groups relevant to the study of childhood leukemia included the Children's Cancer Group (CCG) and the Pediatric Oncology Group (POG), who were the first cooperative groups to conduct clinical trials specific for infant ALL.

CCG trials

The first infant-specific CCG trials were based on a preceding pilot study for patients with poor prognosis ALL, CCG-192P, that enrolled 27 infants from 1982 to 1984. This pilot followed a retrospective review of 115 infants treated on preceding noninfant-specific protocols between 1972 and 1982 that revealed a dismal 4-year EFS (23%) because of disease recurrence rather than excessive toxicity.[12] The premise of CCG-192P was intensification of multiagent chemotherapy, administered in three phases using weight-based dosages, to prolong remission and ultimately survival, with delayed central nervous system (CNS) prophylaxis of 1800 cGy cranial radiation until patients were $\geqslant 1$ year of age.[13] Complete remission (CR) following induction was achieved in 92.6% and no differences in toxicity were observed compared with older children on the same protocol. There was a 36% 4-year EFS with four CNS relapses, all of whom had received cranial irradiation. Univariate analysis revealed a more favorable outcome for infants with a white blood cell (WBC) count $<50\times10^3/\mu$l and age >6 months at diagnosis.[13]

CCG-107 enrolled 98 evaluable infants between 1984 and 1988 and CCG-1883 enrolled 135 evaluable infants between 1989 and 1993. Both studies intensified systemic chemotherapy, administered in five phases with dosages calculated on body surface area, and introduced high-dose methotrexate with intrathecal chemotherapy for CNS prophylaxis. CCG-1883 was further intensified post induction, primarily with the addition of high-dose cytarabine. CR was achieved for 87.8% on CCG-107 and 94.1% on CCG-1883.[14] There was an improvement in 5-year EFS (37.6% vs 32.6%) and OS (50.2% vs 42.8%) when comparing CCG-1883 with CCG-107,[15] with tolerable toxicities. However, the 5-year disease-free survival (DFS) on CCG-1883 remained low (38.5%),[16] with a high overall relapse rate in both studies (CCG-107, 59.2%; CCG-1883, 55.6%). Isolated marrow relapse was the most common cause of treatment failure (CCG-107, 35.7%; CCG-1883, 40.7%). The majority of first relapses occurred early (within 13 months of diagnosis) and was the primary cause of death.[14] Nevertheless, the probability of isolated CNS relapse on CCG-1883 was lower (3.0%) as compared with CCG-107 (8.2%),[15] and was similar to a historical control (CCG-160) that used cranial radiotherapy (5%).[14] This led to the conclusion that compared with cranial radiotherapy, the combination of intrathecal and high-dose systemic therapy represented a superior and effective treatment strategy for prevention of CNS disease, with improved neurodevelopmental outcome.[14,17] Analysis of combined data from both studies identified several prognostic factors associated with poor outcome, including age <6 months at diagnosis, with the most inferior outcome in those <3 months, CD10 negativity, failure of morphological remission on day 14 marrow, WBC $>50\times10^9$/l at diagnosis and presence of the t(4;11) *MLL* rearrangement.[14]

The subsequent study, CCG-1953, aimed to improve the overall poor outcome and reduce the early relapse rate shown in the preceding studies via introduction of early treatment intensification, with dosages based on body surface area and elimination of age-related dose reductions. In addition, the feasibility and outcome of allogeneic hematopoietic stem cell transplantation (HSCT) was examined for *MLL*-rearranged infants for whom HSCT could be scheduled by 4 months of study entry and a 5–6/6 human leukocyte antigen related or unrelated matched donor was available. Overall, 115 infants were enrolled between 1996 and 2000.[16] As a consequence of excessive infectious induction toxicity, the daunorubicin dosage during induction was modified, calculated on weight and age at diagnosis, and for infants $\leqslant 90$ days of age at diagnosis, daily short rather than continuous infusion was implemented. CR was achieved in 82.5% of the infants.[16] Compared with CCG-1883, there was an improved 5-year EFS (43.2%)[15] and DFS (49.2%),[16] but slightly lower 5-year OS (46.8%).[15] The improvements were especially marked when comparing 5-year EFS (41.7% vs 9.5%) and DFS (56.3% vs 11.1%) for infants younger than 90 days of age at diagnosis. There was a significant difference in 5-year EFS between *MLL*-rearranged

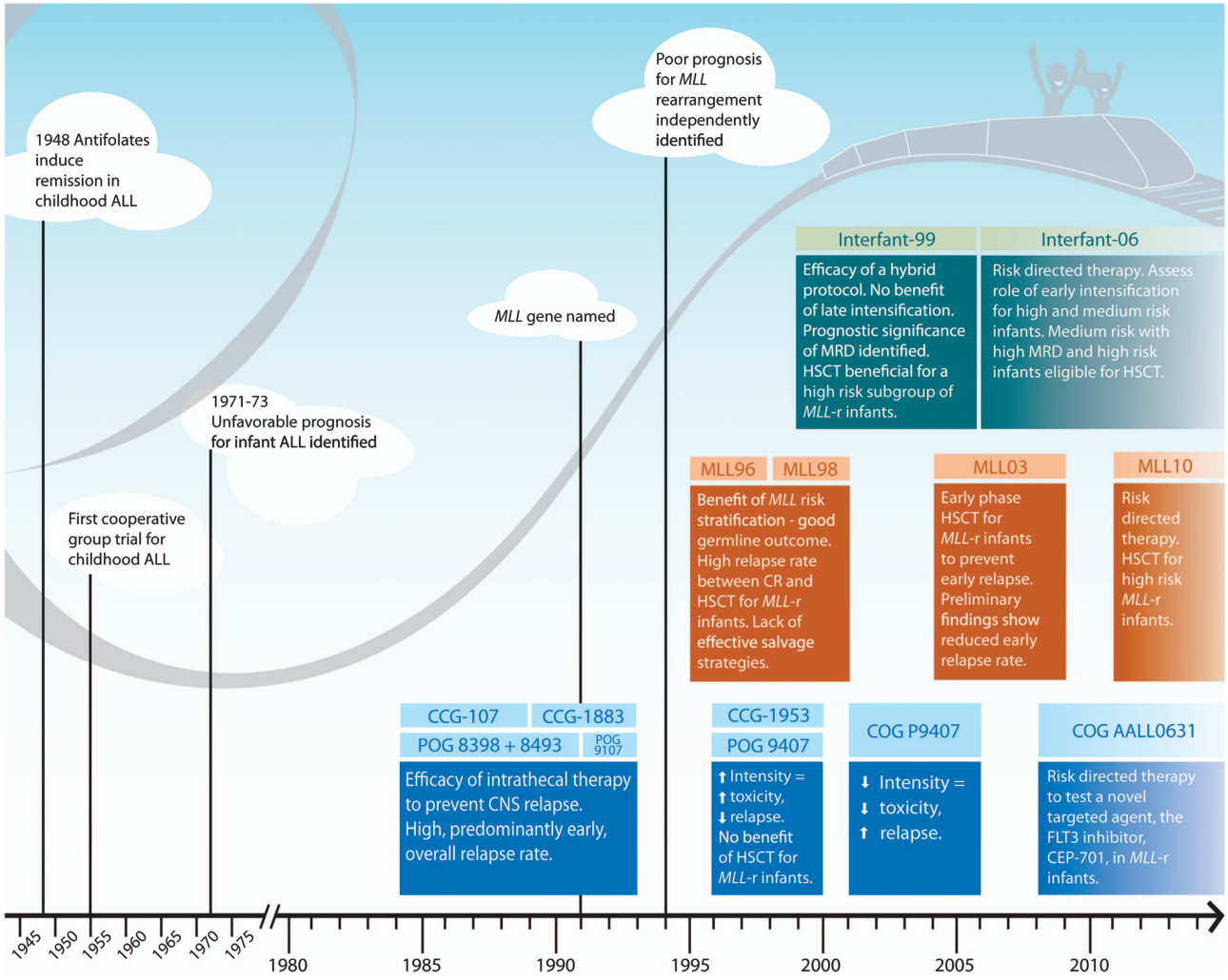

Figure 1. The roller coaster journey of infant ALL.

(33.6%) and *MLL*-nonrearranged cases (60.3%) when prognostic factors were considered individually; however, CD10 negativity was the only independent adverse prognostic factor identified.[16] The key finding of CCG-1953 was that despite fewer relapses (20.9% vs 55.6%), no isolated CNS relapses,[15] and relapses occurring later compared with CCG-1883,[16] the remission induction rate was inferior because of early, predominantly infectious, toxicity.[18]

POG trials

The first infant-specific study, POG 8493, enrolled 84 evaluable infants between 1984 and 1990, with the aim of intensifying therapy using pulsed weight-based doses of cyclophosphamide, vincristine, cytarabine and prednisone (COAP) and teniposide and cytarabine. Despite a CR rate of 89.3%,[19] the 5-year EFS (25.0%) and OS (31.6%) were poor, with adverse prognosis on univariate analysis for age <9 months at diagnosis.[20] POG 8493 ran concurrently with the noninfant-specific POG 8398 pilot study that enrolled 33 evaluable infants. POG 8398 was designed to address early relapse with intensive early consolidation and prevent drug resistance by using rotating drug pairs during this phase. Drug pairs selected included intermediate-dose methotrexate and 6-mercaptopurine, daunorubicin and cytarabine, and teniposide and cytarabine.[21] CR was achieved in 93.9%, but 5-year EFS (17.7%) and OS (36.4%) remained poor.[19]

POG 9107 further evaluated postinduction rotating cycles of intensive, weight-based dosing, combination chemotherapy comprising high-dose cytarabine and daunorubicin, intravenous 6-mercaptopurine and methotrexate, etoposide and cytarabine, and COAP with the aim to reduce bone marrow relapse rate with early intensification. There were 47 evaluable infants enrolled between 1991 and 1993, with CR achieved in 89.4% and an improved 5-year EFS (31.9%) and OS (40.2%). Triple intrathecal therapy was used as CNS prophylaxis for all three studies with a low cumulative incidence of isolated CNS relapse on POG 8398/8493/9107 of 3.4% at 10 years. However, there was a high overall relapse rate (59.8%), with marrow relapse being the primary cause of treatment failure.[19] When analyzed in combination, WBC $>50\times10^3/\mu l$ at diagnosis was identified as the only independent prognostic variable predictive of adverse outcome, with presence of the t(4;11) *MLL* rearrangement tending to predict poorer outcome.[19]

POG 9407 delivered shortened (46 weeks) intensified therapy, with dosages based on body surface area, using two high-dose methotrexate courses followed by one cyclophosphamide/etoposide course during induction and later as reintensification, with the aim of improving outcome by decreasing early relapse. HSCT was permitted for *MLL*-rearranged infants following completion of reinduction. Cohort 1 enrolled 16 infants between 1996 and 1997, with daunorubicin administered during induction and reinduction as a body surface area-based 48-h continuous infusion. Due to

Table 2. Summary of results for infant-specific collaborative group ALL protocols

Group	*Study*	*Year*	*Number analyzed*	*CR (%)*	*5-Year EFS (%)*	*5-Year OS (%)*	*Reference*	*Key conclusions*
CCG	CCG-107 CCG-1883	1984–1988 1989–1993	98 135	87.8 94.1	32.6 37.6	42.8 50.2	14,15	• Progressive improvement in outcome with intensified therapy • Marrow relapse primary cause of treatment failure • Intrathecal and high-dose systemic therapy superior treatment strategy for prevention of CNS relapse compared with cranial radiotherapy • Age <6 months, CD10$^-$, failure of morphological remission on day 14, WBC $>50\times10^9$/l at diagnosis and presence of t(4;11) *MLL* translocation identified as adverse prognostic factors
	CCG-1953	1996–2000	115	82.5	43.2	46.8	15,16	• Early intensification reduced relapse rate but increased toxicity • CD10$^-$ identified as an independent adverse prognostic factor • No benefit in the routine use of HSCT for *MLL*-rearranged infants
POG	POG 8493 POG 9107	1984–1990 1991–1993	84 47	89.3 89.4	25.0 31.9	31.6 40.2	19	• Early intensification using rotating cycles of combination chemotherapy showed progressive modest improvement in survival but outcomes remained poor • Marrow relapse primary cause of treatment failure • Low rate of isolated CNS relapse with triple intrathecal therapy • WBC $>50\times10^3/\mu$l at diagnosis identified as an independent adverse prognostic factor
	POG 9407 (cohorts $1+2$)	1996–2000	68	—	47.0	53.0	22	• Early intensification reduced relapse rate but increased toxicity • No benefit in the routine use of HSCT for *MLL*-rearranged infants
COG	P9407 (cohort 3)	2001–2006	141	—	42.3	53.0	22	• Therapeutic modifications reduced toxicity but increased relapse rate compared with cohorts 1 and 2
JILSG	MLL96	1995–1998	55	94.1	50.9	60.5	37,39	• Infants with germline *MLL* highly curable with chemotherapy alone (95.5% 5-year EFS and OS) showing benefit of risk-stratification by *MLL* status • High proportion of relapses between first CR and HSCT in *MLL*-rearranged infants suggesting need for more effective postremission therapy • Age <6 months at diagnosis identified as an independent adverse prognostic factor for *MLL*-rearranged infants • Failure to achieve remission following salvage therapy identified as an independent adverse prognostic factor for recurrent/refractory *MLL*-rearranged disease
	MLL98	1998–2001	47					
UK CLWP	Infant 87	1987–1999	40	92.5	22.5[a]	30[a]	42,43	• Significant treatment related toxicity and high relapse rate despite increased therapeutic intensity • Age <6 months, presence of CNS disease and hyperleukocytosis at diagnosis identified as independent adverse prognostic factors
	Infant 92		86	94.2	29[a]	42.5[a]		
Interfant	Interfant-99	1999–2005	483	93.9	46.1	55.2	44–47	• Efficacy of a hybrid protocol demonstrated • *MLL* rearrangement, age <6 months at diagnosis and poor day 8 prednisone response identified as independent adverse prognostic factors • No benefit from adding a late intensification course • Prognostic impact of MRD following induction and consolidation identified • Risk of relapse significantly higher for congenital ALL • HSCT beneficial for MLL-rearranged infants aged <6 months and poor day 8 prednisone response or WBC ≥300 g/l at diagnosis

Abbreviations: ALL, acute lymphoblastic leukemia; CCG, Children's Cancer Group; CNS, central nervous system; COG, Children's Oncology Group; CR, complete remission; EFS, event-free survival; HSCT, hematopoietic stem cell transplantation; JILSG, Japan Infant Leukemia Study Group; *MLL*, *mixed lineage leukemia*; MRD, minimal residual disease; OS, overall survival; POG, Pediatric Oncology Group; UK CLWP, United Kingdom Childhood Leukemia Working Party; WBC, white blood cell count. [a]6-year EFS and OS; UK CLWP studies included 9 patients between 12 and 18 months of age with biological features of infant ALL.

excessive toxicity, the same amendments for CCG-1953 regarding daunorubicin during induction were made for cohort 2 that enrolled 52 infants between 1997 and 2000. For the 68 infants, the 5-year EFS and OS were 47% and 53%, respectively.[22] However, there was a high early death rate (25%), defined as within 90 days of enrollment, particularly among infants $\leqslant$90 days of age (58.8% vs 13.7%), with the majority of deaths attributable to infection.[22]

A total of 53 patients underwent HSCT on the parallel CCG-1953 and POG 9407 studies (Table 3). HSCT was the preferred treatment for infants with *MLL* rearrangements on CCG-1953, whereas on POG 9407 transplantation was an investigator option. HSCT according to the protocol-specified conditioning, consisting of cytarabine, cyclophosphamide, methylprednisolone and total body irradiation, was undertaken in 25 cases, whereas the remainder followed nonprotocol-specified regimens. Median time to transplant from first CR was 4.7 months (range 3–13). The 5-year EFS (48.8%) and OS (53.1%) were comparable to a control group of 47 *MLL*-rearranged infants who were enrolled on study but did not receive HSCT (5-year EFS 48.7%, 5-year OS 59.4%), suggesting no benefit in the routine use of HSCT for infants with *MLL*-rearranged ALL.[23]

COG trials

The COG continued the premise of POG 9407, enrolling 141 infants on P9407 cohort 3 from 2001 to 2006. Modifications aimed to reduce toxicity and included substitution and relative dose reduction of steroid during induction, reinduction and continuation (dexamethasone 10 mg/m^2 per day replaced with prednisone 40 mg/m^2 per day) and substitution of the continuous with daily short daunorubicin infusions during induction and reinduction for all infants. In addition, extensive supportive care recommendations were provided. Compared with the preceding cohorts, a reduction in the early death rate (5.7%) for all age groups was offset by a significantly increased overall relapse rate (37.6% vs 17.6%),[22] resulting in unchanged 5-year EFS (42.3%) and OS (53%).

AALL01P1, a limited institution pilot study, opened in 2002. It aimed to demonstrate the feasibility of an augmented intensive regimen with a dexamethasone-based induction and augmented consolidation followed by a modified augmented Berlin–Frankfurt–Münster (BFM) regimen for infants who did not undergo HSCT. However, this study closed in 2003 because of poor accrual.

The current COG trial, AALL0631 (http://clinicaltrials.gov/ct2/show/NCT00557193), opened in 2008 and incorporates risk-directed therapy according to significant prognostic factors identified from combined analysis of the three 9407 cohorts. Infants are classified as standard risk (*MLL*-nonrearranged), intermediate risk (*MLL*-rearranged, $\geqslant$90 days at diagnosis) or high risk (*MLL*-rearranged, $<$90 days at diagnosis). Initially, therapy was a modified COG P9407-based induction. As a result of excessive toxicity, the study was amended for all infants to receive an Interfant-99-based induction, modified to eliminate the steroid taper, reduce all nonintrathecal chemotherapy doses by 25% for infants $<$7 days old at diagnosis and introduce enhanced supportive care guidelines.[24,25] The postinduction chemotherapy backbone is based on P9407 with an extended continuation to deliver therapy for a total of 2 years to all patients, with the aim to reduce late relapse seen on P9407. More intensive postinduction chemotherapy for *MLL*-rearranged infants has the goal of reducing the high proportion of relapses reported during continuation for *MLL*-rearranged infants on P9407.

AALL0631 is the first collaborative group trial to incorporate a novel targeted therapy for infant ALL. Following a successful drug safety and activity phase,[26,27] *MLL*-rearranged infants were randomized to receive the highly selective small molecule Fms-like tyrosine kinase 3 (FLT3) inhibitor, CEP-701. High FLT3 protein levels are expressed in the leukemic blasts of infants with *MLL*-rearranged ALL,[28] even in the absence of *FLT3* activating mutations, which occur in $<$20% of infants with *MLL*-rearranged ALL.[29–31] Due to drug supply limitations, a subsequent amendment ensures that all newly enrolled *MLL*-rearranged infants receive CEP-701, with a decrease in the overall duration of CEP-701 therapy.

Japanese Pediatric Leukemia/Lymphoma Study Group

The JPLSG was founded in 2003 and became the single collaborative group unifying Japan in 2010 following complete amalgamation of the Tokyo Children's Cancer Study Group (TCCSG), the Japanese Children's Cancer and Leukemia Study Group (JCCLSG), the Japan Association of Childhood Leukemia Study (JACLS) and the Kyushu Yamaguchi Children's Cancer Study Group (KYCCSG). However, a unified approach for the study of infant leukemia in Japan had commenced before formation of the JPLSG under the guise of the Japan Infant Leukemia Study Group (JILSG).

The JILSG were the first group to study the effectiveness of risk-adapted therapy according to the presence or absence of *MLL* rearrangements, based on this being identified as the most important prognostic factor for infant ALL.[9,32–34] Two consecutive protocols, MLL96 and MLL98, enrolled 102 infants between 1995 and 2001.[35–37] *MLL*-rearranged infants received induction and three courses of postremission intensification followed by HSCT, with protocol-specified conditioning comprising either total body irradiation or busulfan, etoposide and cyclophosphamide, if a 5–6/6 human leukocyte antigen-matched related, 6/6-matched

Table 3. Summary of results for allogeneic HSCT in first CR in clinical trials for infant ALL

Group	*Study*	*Year*	*Number with HSCT in first CR*	*Outcome post HSCT*			*Reference*
				Continued first CR	*Death in CR*	*Relapse*	
CCG	CCG-1883	1989–1993	12	2	5	5	14
UK CLWP	Infant 87/92	1987–1999	15	5	3	7	42,43
AIEOP	AIEOP-ALL 91/95	1991–2000	6	3	3	0	111
JILSG	MLL96/98	1995–2001	47	27	8	12	37
COG	CCG-1953/POG 9407	1996–2000	53	27	17	9	23
Interfant	Interfant-99	1999–2005	37	21	2	14	45
	Total	1987–2005	170	85	38	47	

Abbreviations: AIEOP, Associazione Italiana Ematologia Oncologia Pediatrica; ALL, acute lymphoblastic leukemia; CCG, Children's Cancer Group; COG, Children's Oncology Group; CR, complete remission; HSCT, hematopoietic stem cell transplantation; JILSG, Japan Infant Leukemia Study Group; UK CLWP, United Kingdom Childhood Leukemia Working Party.

unrelated or 4–6/6-matched cord blood donor was available. Infants with germline *MLL* received intensive chemotherapy administered over 83–85 weeks. Aside from vincristine, drug dosages were calculated on body surface area for MLL98 as compared with weight for MLL96. Despite resulting in a 1.2- to 2-fold increase in dosage for MLL98, this was not associated with improved outcome.[37]

For all 102 infants, CR was achieved in 94.1%, with 5-year EFS and OS of 50.9% and 60.5%, respectively.[37] These studies were fundamental in demonstrating the benefit of risk-adapted therapy according to *MLL* status, with outcomes significantly better for infants with germline *MLL* compared to those with *MLL*-rearranged disease. There were 22 infants with germline *MLL* who were highly curable, all achieving CR, with 5-year EFS and OS of 95.5%.[38] In contrast, although the 80 *MLL*-rearranged infants achieved a similar CR rate (92.5%), the 5-year EFS and OS were 38.6% and 50.8%, respectively. Of the 74 *MLL*-rearranged infants who achieved CR, 53 remained in CR during the postremission phase, with 47 undergoing allogeneic HSCT (Table 3), 2 receiving high-dose chemotherapy and autologous stem cell rescue and 4 with no suitable donor who remained in CR with chemotherapy alone.[37] The median time to transplant from first remission was 4 months (range 0–9).

Relapse occurred in 34 *MLL*-rearranged infants, with isolated bone marrow relapse occurring in 30 and 2 isolated CNS relapses. Another key conclusion from these studies was the need for more effective postremission therapy, as a high proportion of relapse (61.7%, $n = 21/34$) occurred before HSCT.[39] Age <6 months was the only independent prognostic factor associated with inferior outcome for *MLL*-rearranged infants (5-year EFS 27.8% <6 months vs 52.9% $\geqslant 6$ months) with CNS disease at diagnosis identified on univariate analysis.[37] Compared with the germline group, univariate analysis demonstrated that *MLL*-rearranged infants were significantly younger, had higher WBC counts, increased frequency of CNS disease and CD10 negativity at diagnosis.[37]

MLL03 built on findings of the preceding studies with the aim of early phase ($\leqslant 4$ months after first CR) HSCT to prevent early relapse for *MLL*-rearranged infants. The study recruited 63 infants between 2004 and 2009. Therapy consisted of a 7-day prednisolone prophase followed by induction that included dexamethasone, vincristine, doxorubicin, cyclophosphamide, cytarabine, etoposide and triple intrathecal therapy, followed by two intensification courses including high-dose methotrexate and high-dose cytarabine. If CR was achieved and a $\geqslant$5/6-matched related or $\geqslant$4/6-matched unrelated cord blood donor was available, HSCT was performed using a busulphan, etoposide and cyclophosphamide protocol-specified conditioning. Preliminary data have shown 18-month EFS and OS of 54.5% and 80.8%, respectively,[40] with a reduced early relapse rate, occurring in 3 patients before HSCT compared with 21 patients following HSCT.[41]

The aim of the current JPLSG study, MLL10 (https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&recptno=R000005714&language=E), which opened in 2011, is to evaluate the efficacy and safety of risk-directed therapy using a new stratification system. *MLL* germline infants are classified low risk and treated with the MLL96/98 chemotherapy backbone. *MLL*-rearranged infants $\geqslant 180$ days of age with no CNS disease are intermediate risk and treated with intensive combination therapy without HSCT in first CR. *MLL*-rearranged infants <180 days of age or with CNS disease are deemed high risk and treated with intensive combination therapy with HSCT in first CR.

Interfant Study Group

The Interfant Study Group is a large international collaborative dedicated to infant ALL research, with representation from the Dutch Childhood Oncology Group (DCOG), BFM study group, Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP), Australian and New Zealand Children's Hematology/Oncology Group (ANZCHOG), European Organization for Research and Treatment of Cancer–Children's Leukemia Group (EORTC-CLG), Co-operative study group for treatment of ALL (CoALL), Czech Pediatric Hematology working group (CPH), French Acute Lymphoblastic Leukemia group (FRALLE), Nordic Society of Pediatric Hematology and Oncology (NOPHO), Programa Infantil Nacional de Drogas Antineoplásicas (PINDA), Polish Pediatric Leukemia and Lymphoma Study Group (PPLLSG), United Kingdom Children's Cancer and Leukemia Group (CCLG), St Jude Children's Research Hospital, Dana-Faber Cancer Institute consortium, MD Anderson Cancer Center and centers from Seattle, Argentina and Hong Kong.

Before formation of the Interfant Study Group, the UK Medical Research Council Childhood Leukemia Working Party, now operating as the CCLG, conducted two infant-specific studies. Infant 87 was a pilot study designed to increase the intensity of therapy from the preceding risk-adapted UKALL trials, with inclusion of drug combinations with recognized actions against acute myeloid leukemia and to provide effective CNS-directed therapy without cranial irradiation. Drug dosages were calculated on body surface area. A four-drug induction was followed by 5 days of etoposide and cytarabine, with three subsequent high-dose methotrexate infusions. Further intensification was given with mitoxantrone and cytarabine followed by a further reinduction course.[42] Subsequent therapy was not standardized and options included HSCT for infants with a matched sibling donor, high-dose chemotherapy and autologous stem cell rescue or standard continuation. The study enrolled 40 infants with CR achieved in 92.5%. Despite increased intensity of therapy, there was no improvement in survival (6-year EFS, 22.5%; 6-year OS, 30%) compared with infants enrolled on the preceding risk-adapted UKALL protocols, with a high number of toxic deaths especially following the 5-day course of etoposide and cytarabine. There was a high overall relapse rate of 47.5%, with isolated marrow relapse accounting for 37.5% and isolated CNS relapse 5%.[43] Outcome for 8 infants who underwent high-dose chemotherapy followed by autologous stem cell rescue was not encouraging, with 5 suffering bone marrow relapse.

The subsequent study, Infant 92, enrolled 86 patients between 1992 and 1999. As a result of excessive toxicity on Infant 87, modifications included a reduction in the duration of etoposide and cytarabine from 5 to 4 days, interim maintenance rather than reinduction at week 20, followed by an 8-week delayed intensification before continuation.[43] HSCT was permitted for *MLL*-rearranged infants with a matched donor. CR was achieved in 94.2% with a modest improvement in 6-year EFS (29%) and OS (42.5%). However, there remained a high overall relapse rate (55.8%), and despite a slight reduction in the isolated marrow relapse rate (32.6%), there was an increase in the isolated CNS relapse rate (11.6%).[43] There was no difference in EFS for the 12 patients who underwent HSCT in first remission compared with those who had chemotherapy alone. CNS disease, age <6 months and higher WBC count at diagnosis were independently associated with an adverse prognosis following combined analysis from both studies.[43]

The first trial of the Interfant Study Group, Interfant-99, enrolled 483 infants between 1999 and 2005.[44,45] This study continued with a hybrid treatment schedule comprising elements used to treat both ALL and acute myeloid leukemia, while minimizing the use of anthracyclines and alkylating agents. Based on results of infants enrolled onto preceding BFM studies,[11] all infants received a 7-day prednisone prophase with stratification into standard- and high-risk groups determined by day 8 peripheral blood blast count ($</\geqslant 1000$ cells/μl, respectively). High-risk infants had the option of receiving HSCT at the end of reinduction if a suitable donor was

available, otherwise they were scheduled to have cytarabine and etoposide added to their standard maintenance. The protocol administered age-based dosing calculated on body surface area. CR was achieved in 93.9% of 474 evaluable infants at the end of induction.[44] The 5-year EFS and OS were 46.1% and 55.2%, respectively.[45] *MLL* germline infants had the best outcome, with 5-year EFS of 74.0%. Overall relapse rate was 34.4%, with isolated marrow relapse accounting for 25.7% and isolated CNS relapse 2.5%,[44] with significantly higher risk of relapse identified for congenital leukemia.[46] Independent prognostic factors associated with an inferior outcome included presence of an *MLL* rearrangement, age <6 months at diagnosis and poor prednisone response at day 8, with CD10 negativity and WBC $\geqslant 300 \times 10^9$/l at diagnosis also identified on univariate analysis. A higher proportion of infants <6 months of age at diagnosis were *MLL* rearranged, with the majority of t(4;11) and t(11;19) translocations occurring in this group, whereas the majority of t(9;11) translocations occurred in infants aged 6–12 months at diagnosis.[44]

Interfant-99 also assessed the efficacy of late intensification comprising vincristine, 6-mercaptopurine, high-dose methotrexate, high-dose cytarabine, asparaginase and additional triple intrathecal therapy, with 191 eligible infants randomized to receive this course between reinduction and maintenance. There was no difference in outcome, with substantial toxicity associated with this additional intensification phase.[44]

The prognostic significance of minimal residual disease (MRD), analyzed by real-time quantitative PCR analysis of rearranged immunoglobulin/T-cell receptor genes and/or *MLL* genes, was tested in 99 infants following induction and consolidation. High MRD was significantly associated with lower DFS. All infants who had MRD $\geqslant 10^{-4}$ following consolidation relapsed, whereas the lowest relapse rate (13%) was seen in patients who had MRD $<10^{-4}$ following induction and consolidation. All *MLL* germline infants had MRD $<10^{-4}$ following consolidation and remained in remission.[47]

There were 37 *MLL*-rearranged infants who underwent HSCT at a median time of 5 months (range 2–9) from first CR (Table 3). A preparative regimen of busulfan, etoposide and cyclophosphamide was advised, but donor selection, conditioning and graft versus host disease prophylaxis and treatment were not mandated. When compared with 240 *MLL*-rearranged infants who received chemotherapy alone after first CR, there was significantly improved DFS and OS for a subgroup of high-risk *MLL*-rearranged infants with unfavorable prognostic features, including age <6 months and either poor day 8 prednisone response or WBC $\geqslant 300$ g/l at diagnosis, although this subgroup also had a high early failure rate, with a third having an event before the median time to transplantation.[45]

The current study, Interfant-06 (http://clinicaltrials.gov/show/NCT00550992) commenced enrollment in 2006 and, based on results of Interfant-99, stratifies infants into low risk (*MLL* germline), high risk (*MLL*-rearranged and age <6 months and WBC $\geqslant 300 \times 10^9$/l at diagnosis and/or poor day 8 prednisone response) and medium risk (all other cases). The study aims to assess early intensification to improve outcome and prevent early relapse, as opposed to the late intensification considered for Interfant-99. High- and medium-risk infants are randomized to two 'acute myeloid leukemia' induction blocks (cytarabine, daunorubicin and etoposide; cytarabine, mitoxantrone and etoposide) versus the control arm, also specified for all low-risk infants, comprising BFM IB (6-mercaptopurine, cytarabine, cyclophosphamide) following induction, with medium-risk infants with MRD $\geqslant 10^{-4}$ following consolidation and all high-risk infants also eligible for HSCT after consolidation. The remainder of therapy is similar to Interfant-99, with the main modifications including intensification of asparaginase therapy and removal of dexamethasone and vincristine during maintenance.

Summary of outcomes from the infant-specific protocols

A wealth of information has been gleaned from the infant-specific clinical trials. Concise outcomes for each study are summarized in Table 2, including a number of landmark findings that underpin our current therapeutic approaches for infant ALL (Figure 1). An essential early discovery, with subsequent universal adaptation by each of the study groups, was the use of intrathecal and high-dose systemic therapy, with the elimination of cranial radiotherapy, for prevention of CNS disease with improved neurodevelopmental outcome. Second, nowhere has the balance between treatment efficacy and toxicity been better demonstrated than for infant ALL, where the infant-specific trials have varied in therapeutic intensity, with recent survival outcomes unchanged due to the equilibrium between relapse and toxicity (Figure 1). Analysis of outcomes drawn from this conclusion has led to beneficial chemotherapeutic features identified from prior trials being uniformly incorporated into contemporary studies. These include the adoption of an Interfant-99-based induction given its satisfactory CR rate and acceptable toxicity profile, the necessity of an extended continuation to prevent late relapse and mandating enhanced aggressive supportive care measures to minimize risk of infection. Current published data, however, do not reveal a superior chemotherapeutic backbone on which to base future trials for *MLL*-rearranged infants, with similar EFS across each of the collaborative groups (CCG-1953: 33.6%, 5-year EFS[16]; JPLSG MLL96/98: 38.6%, 5-year EFS[37]; Interfant-99: 36.8%, 4-year EFS[45]), although additional insight may be provided following results of the contemporary treatment protocols. Finally, the universal prospective identification of independent adverse prognostic factors, including presence of an *MLL*-rearrangement and young age, has resulted in such variables forming a standard component of risk stratification in each of the current trials. It is these landmark outcomes that provide the foundation for the next generation of clinical trials for infant ALL.

THE FUTURE: THE NEXT GENERATION OF TRIALS FOR INFANT ALL

Substantial therapeutic advances have been made for infant ALL since the first pediatric cooperative group ALL trials were conceived. Key events include the identification of inferior outcome for infants compared with older children, discovery of prognostic features within infant ALL, in particular the dismal outcome associated with an *MLL* rearrangement, formation of the three large collaborative groups dedicated to the study of infant ALL with treatment on infant-specific protocols and incorporation of risk-directed therapy according to prognostic features (Figure 1). Although there has been an increase in survival over time, this is predominantly attributable to the improved outcome of infants with germline *MLL*. Survival for *MLL*-rearranged infants remains significantly inferior to older children and we are approaching the limit for which conventional chemotherapeutic agents can be intensified to optimize the balance between relapse and toxicity. Globalization combined with the recent explosion of molecular data have provided the armamentarium for the next generation of clinical trials for infant ALL. A number of key issues require addressing in future trials to ultimately translate into improved outcome.

The role of HSCT in first complete remission

Although each of the infant-specific ALL study groups have attempted to prospectively define the role for HSCT in first CR, no clear consensus has been drawn.[23,36,37,45] Differing conclusions from preceding studies have consequently led to differences between study groups regarding the role of HSCT within current infant-specific protocols. The combined prospective study data do not appear to demonstrate additional benefit for HSCT in first CR

(Table 3); however, these data are reflective of a heterogeneous infant ALL population treated with diverse HSCT protocols over different time periods. The absence of randomized controlled study designs to compare HSCT with chemotherapy alone further adds to the limitations of the available prospective data. A number of retrospective reports have mirrored such findings, demonstrating both advantage[48–51] and no clear benefit[52–55] of HSCT in first CR for infant ALL. Such conflicting results may be attributable to the small number of patients who have undergone HSCT within each study and the marked variability of transplant protocols used. Although it is accepted that HSCT should not be administered for *MLL* germline cases in first CR, the subgroup of *MLL*-rearranged infants for whom HSCT in first CR could be definitively performed, the optimal timing at which HSCT should be undertaken and the most suitable transplant protocol remain to be defined. However, on the basis of this review, we conclude that currently there is insufficient evidence to support the use of HSCT in first CR for infant ALL.

Identification of novel prognostic markers and adaptation of innovative therapies

The *MLL* gene was named in 1991,[56,57] and considerable research has subsequently been dedicated to the molecular mechanisms underlying oncogenesis for *MLL*-rearranged infant leukemia. The explosion of scientific discovery associated with recent technological advances has enabled identification of additional molecular prognostic markers, novel targets and development of innovative therapies. Molecular markers recently identified as independent predictors of poor prognosis for *MLL*-rearranged infant ALL include *RAS* mutations,[58] low FAS expression,[59] absence of *HOXA* expression[60] and using gene expression profiling-based gene classifiers.[61] The challenge underlying the wealth of prognostic characterization, however, is to identify the most appropriate candidates for integration into future clinical trials.

The FLT3 inhibitor, CEP-701, is the first novel agent investigated in a large collaborative clinical trial for *MLL*-rearranged infant ALL. There are numerous other drug candidates tested in infant-specific preclinical models with translational potential. These include drugs targeting the aberrant epigenetic profile identified in *MLL*-rearranged infant ALL. An overall global hypermethylated state has been identified for t(4;11), t(11;19) and t(9;11) rearranged infants[62] and promoter CpG island hypermethylation in t(4;11) and t(11;19) rearranged infants with subsequent silencing of transcriptional genes and microRNAs.[63–65] Several studies have demonstrated *in vitro* efficacy of demethylating agents, such as decitabine, zebularine and 5-azacitidine.[62–66] In addition, hypomethylation has been demonstrated in a subset of highly expressed proto-oncogenes in t(4;11) rearranged infants with *in vitro* response to histone deacetylase inhibitors.[67]

Overexpression of members of the antiapoptotic B-cell lymphoma 2 family have been identified in *MLL*-rearranged infant ALL.[68,69] B-cell lymphoma 2 inhibition provides a promising therapeutic strategy with *in vitro* activity demonstrated for obatoclax,[70] ABT-737,[71] and G3139.[68] Another approach includes targeting the constituently activated Janus kinase/signal transducer and activator of transcription signaling pathway identified in CD10-negative infant ALL, with effective apoptosis of cells *in vitro* using the Janus kinase 3 inhibitor, WHI-P131 and the pan-Janus kinase inhibitor, AG-490.[72] *In vitro* inhibition of the phosphatidylinositide 3-kinase/AKT/mammalian target of rapamycin signaling pathway has identified compounds such as thioridazine worthy of further investigation.[73] *In vivo* studies include potent single agent activity of the antibody-drug conjugate, SAR3419, in infant-*MLL* xenografts expressing CD19,[74] and *in vivo* efficacy of the p53-MDM2 inhibitor, RG7112, as a single agent and in combination with an induction-type chemotherapy regimen.[75]

An alternative approach to targeted therapy is to use novel or existing agents to enhance the efficacy of conventional therapeutics. This includes overcoming glucocorticoid resistance using Src kinase inhibitors[76,77] and phosphatidylinositide 3-kinase inhibitors[78] *in vitro* and enhancing the efficacy of CEP-701 via CXCR4 inhibition using plerixafor *in vivo*.[79]

In addition, there are numerous exciting new candidates exhibiting potency in noninfant ALL-specific *MLL*-rearranged preclinical studies such as inhibitors of DOT1L,[80,81] menin[82] and AMP-activated protein kinase[83] that remain primed for testing in infant ALL-specific preclinical models.

However, incorporating novel agents into clinical trials is fraught with translational barriers. A number of strategies are being addressed to overcome the classic translational roadblocks,[84] and it is imperative to have commitment from stakeholders once an agent is considered for a clinical trial. With recent advances, the future will yield a multitude of potential candidates for testing in the setting of a clinical trial. Although the rarity of infant ALL precludes investigation of every suitable drug, the use of adaptive 'pick a winner' trial designs or assessment of novel agents within the relapsed/refractory disease setting may enable differentiation of the most suitable agent for further investigation.

Treatment strategies for relapsed/refractory disease

Treatment of relapsed/refractory infant ALL constitutes a significant challenge as there is no defined therapy. The absence of an infant-specific relapse study has led to treatment on relapsed childhood ALL protocols or individualized therapy at the discretion of the treating institution. The lack of a uniform centralized approach is reflected by the paucity of outcome measures for relapsed/refractory infant ALL.

The JILSG retrospectively reviewed 39 infants with relapsed ($n = 34$) and refractory ($n = 5$) *MLL*-rearranged ALL from the MLL96 and MLL98 studies.[39] These patients underwent a variety of salvage therapies. CR was achieved in 40.5% and 5-year OS was 25.6%, with failure to achieve remission following second-line therapy identified as the sole independent prognostic factor, and age < 3 months and CNS involvement at initial diagnosis associated with higher risk of failure on univariate analysis.[39] Nine patients received HSCT in second CR, with 5 continuous second remissions, 3 relapses and 1 toxic death. A total of 14 patients received HSCT with active disease, with 2 continuous second remissions, 8 relapse deaths and 4 toxic deaths. One patient who had refractory disease remains in continuous second remission following chemotherapy alone.[39] The poor outcome for *MLL*-rearranged infants with induction failure has also been highlighted in a large international retrospective analysis, with 10-year OS of 4% compared with 65% for *MLL*-nonrearranged infants.[85] The UK CLWP Infant 92 study reported a 6-year OS of 20% for 48 infants who relapsed.[43] A total of 10 patients received HSCT while in second CR, with 3 continuous second remissions, 3 relapses and 4 HSCT-related deaths; however, the *MLL* status of the relapsed patients was not specified. A retrospective single-center analysis found salvage possible in a proportion of patients who achieved CR following relapse with the use of HSCT (3-year EFS, 43%), with dismal outcomes for those receiving HSCT with active disease following relapse (3-year EFS, 6%).[50] Outcomes for *MLL*-rearranged infants, however, were poor in both groups.

In the absence of any defined therapy for relapsed/refractory disease, these limited findings suggest the feasibility of HSCT, provided that CR can be achieved before transplant. It is evident, however, that considerable attention is required for the treatment of relapsed/refractory disease. This may be facilitated through mandatory reporting of such cases to the study groups by the treating institution, establishment of an international registry or a single unified infant-specific trial for relapsed/refractory disease.

Late effects in survivors

There is an increasing recognition of late effects in survivors of infant ALL. Cranial radiation was the main risk factor for development of late effects;[10,86] however, adaptation of high-dose methotrexate and intrathecal chemotherapy as CNS-directed therapy has led to a substantial improvement in neurodevelopmental outcome.[17] Currently, the main contributory factors for the increasing burden of late effects include the increasing number of survivors with time for late effects to be appreciated, increased intensity of therapy, young age at which therapy is delivered and emergence of late effects as a subspecialty. The long-term sequelae attributable to cranial radiation[10,86] and HSCT[37,50] in survivors of infant ALL have been well documented, but there are limited data available for the remainder. Long-term follow-up of survivors should be encouraged in future clinical trials to further identify and characterize the pattern of long-term morbidity and allow for timely intervention.

CONCLUSION

Clinical trials for infant ALL have evolved significantly over time, with each stage providing vital contributions to the biological and therapeutic advances that have been achieved. Despite these advances, survival of infants with ALL continues to remain significantly inferior to older children. We are approaching the limit to which conventional chemotherapy can be intensified with acceptable toxicity to minimize relapse. There is a need to identify and incorporate the most promising drug candidates from preclinical studies into the next generation of clinical trials. Integration of novel molecular prognostic markers, the role of HSCT in first remission, treatment strategies for relapsed/refractory disease and monitoring and timely intervention of late effects require addressing in future trials. The heterogeneity and rarity of infant ALL is the major limitation for clinical trials, resulting in slow accrual over long time periods and limiting study power. Global harmonization and maximization of accrual could be achieved through a unified international trial, involving the three major collaborative infant ALL study groups and engaging missing nations that have the ability to partake.[87] Despite the inherent administrative, legal, drug supply and regulatory difficulties associated with such an approach, feasibility has been demonstrated by a number of global collaborative pediatric cancer trials including the European and American Osteosarcoma Study Group (EURAMOS) trial and the Intergroup trial for B-cell Non-Hodgkin lymphoma/mature B-cell leukemia. Establishment of such a trial would provide greater potential to answer key treatment issues and ultimately lead to improved outcome for infant ALL.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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