Intrachromosomal Amplification of Chromosome 21 in Pediatric Patients with B-Cell Precursor Acute Lymphoblastic Leukemia: A Systematic Review and Meta-Analyses

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Simple Summary: Intrachromosomal amplification of chromosome 21 (iAMP21) is a primary cytogenetic change. iAMP21 defines a distinct cytogenetic subgroup of childhood B-cell precursor acute lymphoblastic leukaemia (BCP-ALL). This review aims to systematically review the incidence, clinical characteristics, and treatment outcome of iAMP21 in B-cell precursor ALL.

Abstract: Intrachromosomal amplification of chromosome 21 (iAMP21) is defined as the presence of three or more RUNX1 signals on one marker chromosome. It is a distinct cytogenetic subgroup of childhood B-cell precursor ALL. iAMP21 is known to have poor prognosis when precursor treated with standard therapy. Data was screened using keywords 'intrachromosomal amplification of chromosome 21", "iAMP21", "leukemia","ALL" using database Pubmed and EuroPMC. A total of 103 records screened and only 9 included in this study. The outcome such as event free survival ranged from 46.9% to 80%. The overall survival of the patients ranged from 64% to 92%. The differences in treatment regimen accounted for this large gap range in event free survival and overall survival.

Keywords: ALL, B-cell precursor, chromosome 21, iAMP21

1. Introduction

In 2003, the United Kingdom National Cancer Research Institute (NCRI) Childhood Leukemia Working Party (CLWP) reported a new genetic entity known as the

intrachromosomal amplification of chromosome 21 (iAMP21) in the B-cell precursor acute lymphoblastic leukemia (BCP-ALL) group [1]. It was detected during routine screening for the presence of ETV6-RUNX1 fusion by fluorescence in situ hybridization (FISH). In patients where the fusion was not present, approximately 2% of the patients showed additional copies of signal specific for the RUNX1 gene [2,3].

iAMP21 is defined as the presence of three or more RUNX1 signals on one marker chromosome or a total of five or more RUNX1 signals per cell. Findings reported that patients with iAMP21 had inferior outcome when treated with standard therapy, compared to other patients on the same protocol [5]. The aim of this study is to systematically review the incidence, clinical characteristics and treatment outcome of iAMP21 in BCP-ALL patients.

2. Methods

2.1 Eligibility Criteria

Studies that were included in this review were acute lymphoblastic leukemia patients that underwent genetic studies to identify the chromosomal abnormalities, iAMP21 prevalence, clinical characteristics and outcome was mentioned. Studies such as case report, review articles, commentaries, letters, studies in which full text was not accessible, studies that are not in English language and studies that are not in pediatric age group were excluded.

2.2 Search Strategy and Study Selection

Keywords such as “Acute Lymphoblastic Leukemia”, “ALL”, “iAMP21”, “intrachromosomal abnormalities of chromosome 21” were used in the systematic search. We used Pubmed and EuroPMC as the database. The title, abstract, and full text of all articles that matched to the search criteria were assessed and those matched and relevant to this study were included. The references of all identified studies were also analyzed (forward and backward citation tracking) to identify other potentially eligible articles. This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

2.3 Data Extraction and Quality Assessment

Extraction of the data was performed independently by two authors. We tabulated the data into standardized forms that included the age, gender, prevalence, study methods, study type and clinical characteristics. The outcome of interest was relapse rate, event free survival and overall survival. Quality of study was assessed using Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies by the National Heart, Lung, and Blood Institute [5,6].

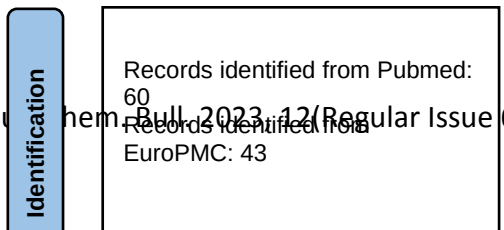

Figure 1. Identification of studies via databases and registers

3. Results

3.1 Study Selection and Characteristics

A total of 103 records were obtained through systematic electronic searches. A total of 78 records were excluded as they were not relevant to the study and did not meet inclusion and exclusion criteria. After screening the full text of 25 records, one was excluded as it was not in English language, a total of 8 studies were included in this systematic review in Table 1. All the studies included were retrospective studies, except one was prospective.

Table 1. A total of 8 studies were included in this systematic review

No.	Clinical trial	Age (years)	Risk group	iAMP ALL prevalence (%)		Treatment outcome	Prevalence from RFS, EFS and OS
1	Jieun Kim et al., 2016 [3]	0-19	High risk	1	1	Clinical course	Relapse 2 times, once after chemotherapy and once directly after bone marrow transplantation
2	Suleimann Al-Sweedan et al., 2019 [11]	<= 14	Standard risk 8, high risk 2	10	2.4	10-year EFS	80.0 ± 17.9
3	Mina Yang et al., 2017 [4]	0 – 18	Standard risk 3, high risk 6, not available 1	10	10	Estimated 10-year cumulative rate of relapse, EFS and OS	53.3%, 46.7% and 64.8% respectively
4	Nyla A. Heerema et al., 2013 [5]	50% age >= 10	High risk 53%	158	2	4 year EFS and OS	72.7% and 92.0%
5	Anthony V. Moorman et al., 2006 [7]	5-9 years 61%, 10+ years 39%	-	28	1.7	5 year EFS and OS	29 (13-48) and 71 (51-84)
6	Anthony V. Moorman et al., 2013 [9]	10.2 (8-11.7)	-	53	2	5 year EFS, relapse rate and OS	78 (61-88), 16 (7-34) and 89 (76-95) respectively
7	Andishe Attarbaschi et al., 2008	9.0 (4.13-16.44)	Low risk 9, Intermediate risk 14,	29	2	6 year EFS and OS	38 ± 14 and 66 ± 11 respectively

	[8]		High risk 1, NA 5				
8	Andishe Attarbaschi et al., 2014 [10]	9.8 (2.8-16.4)	Standard risk 23, High risk 23	46	2	8 year EFS, CIR and OS	64 ± 8, 29 ± 8 and 76 ± 9

CIR: cumulative incidence of relapse; EFS: Event-free survival; OS: overall survival; RFS: Relapse-free survival

3.2 Assessment of the Quality of the Studies

The quality of the study was assessed and shown in Table 2. Studies with retrospective cohort method was assessed and were all rated as good quality.

Table 2. Assessment of the Quality of Studies [3-11]

Study Number	1	2	3	4	5	6	7	8	9
1. Was the research question or objective in this paper clearly stated?	Y	Y	Y	Y	Y	Y	Y	Y	Y
2. Was the study population clearly specified and defined?	Y	Y	Y	Y	Y	Y	Y	Y	Y
3. Was the participation rate of eligible persons at least 50%?	Y	Y	Y	NR	Y	Y	Y	Y	Y
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Y	Y	Y	Y	Y	Y	Y	Y	Y
5. Was a sample size justification, power description, or variance and effect estimates provided?	NR	NR	NR	NR	NR	NR	NR	NR	NR
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Y	Y	Y	Y	Y	Y	Y	Y	Y
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Y	Y	Y	Y	Y	Y	Y	Y	Y
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome	NA	NA	NA	NA	NA	NA	NA	NA	NA

(e.g., categories of exposure, or exposure measured as continuous variable)?									
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Y	Y	Y	Y	Y	Y	Y	Y	Y
10. Was the exposure(s) assessed more than once over time?	N	N	N	N	N	N	N	N	N
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Y	Y	Y	Y	Y	Y	Y	Y	Y
12. Were the outcome assessors blinded to the exposure status of participants?	N	N	N	N	N	N	N	N	N
13. Was loss to follow-up after baseline 20% or less?	N	N	N	N	N	N	N	N	N
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	NA	NA	NA	NA	NA	NA	NA	NA	NA

N: None; NA: Not Applicable; NR: Not Reported

3.3 Outcomes

The frequency of iAMP in BCP-ALL patients range from 1-3.4%. In most of the studies, the patients did not have a high WBC count. The outcome such as event free survival (EFS) ranged from 46.9% to 80%. The overall survival (OS) of the patients ranged from 64% to 92%. All others clinical characteristics are summarized in Table 3 and Table 4.

Table 3. All others clinical characteristics are summarized

Study	Age (years)	Total no of B-ALL	No of iAMP21	Frequency of iAMP21	Diagnostic approach
Jieun Kim et al., 2016 [3]	0-19	102	1	1%	G-banding karyotype, FISH, MLPA
Suleimann Al-Sweedan et al., 2019 [11]	<= 14	411	10	2.4%	FISH
Mina Yang et al., 2017 [4]	0 – 18	295	10	3.4%	FISH
Nyla A. Heerema et al., 2013 [5]	0-18	5057	158	2%	FISH

Anthony V. Moorman et al., 2006 [7]	0-18	1630	28	1.7%	FISH
Anthony V. Moorman et al., 2013 [9]	0-18	2575	53	2%	FISH
Andishe Attarbaschi et al., 2008 [8]	0-20	1625	29	2%	FISH
Andishe Attarbaschi et al., 2014 [10]	1-18	2637	46	2%	FISH

FISH: Fluorescence in situ hybridization; MLPA: Multiplex Ligation-dependent Probe Amplification

Table 4. All others clinical characteristics are summarized

No.	References	ALL	iAMP21	Gender (M/F)	Median age	WBC count ($x10^9$/L)	Specific gene detection method	Study period	Study type
1	Jieun Kim et al., 2016 [3]	102	1	102/0	9	9.16	FISH, MLPA	2009-2015	Retrospective
2	Suleimann Al-Sweedan et al., 2019 [11]	411	10	2/8	5.9 (2.7-13.9)	100% had less than <50k	FISH	2005-2015	Retrospective
3	Mina Yang et al., 2017 [4]	296	10	6/4	9.2 (3.0-13.5)	Median 5 (1 – 8)	FISH	NA	Retrospective
4	Christine J Harrison et al., 2013 [12]	-*	530	255/ 271, unknown` 4	9 (2-30)	Median 5 (0.3-900)	FISH	1987-2011	Retrospective
5	Nyla A. Heerema et al., 2017 [4]	7793	158	Male 3507 Female 4286		95% had WBC < 50k	FISH	2003-2011	Retrospective
6	Nyla A. Heerema et al., 2013 [5]	1630	28	13 15	9 (7.3-13.0)	Median 3.9 (2.6-14.6)	FISH	1997-1999	Retrospective
7	Anthony V. Moorman et al., 2006	2575	53	23/ 30	10.2 (8-11.7)	Median 5.2 (2.5-10.6)	FISH	2003-2011	Prospective

	[7]								
8	Anthony V. Moorman et al., 2013 [9]	1625	29	15/14	9 (4.13-16.44)	Median 10.7 (0.7-67.8)	FISH	1986-2007	Retrospective
9	Andishe Attarbaschi et al., 2008 [8]	2637	46	22/24	9.8 (2.8-16.4)	Median 7.2 (0.7-75.7)	FISH	2000-2010	Retrospective

4. Discussion

To our knowledge, this is the first systematic review that addresses about iAMP21 in BCP-ALL. iAMP21 is a primary cytogenetic change [6]. Intrachromosomal amplification of chromosome 21 (iAMP21) defines a distinct cytogenetic subgroup of childhood B-cell precursor acute lymphoblastic leukaemia (BCP-ALL). iAMP21 is defined as the presence of three or more RUNX1 signals on one marker chromosome or a total of five or more RUNX1 signals per cell. Based on this review, the presence of iAMP21 has a negative impact on the outcome of the patient. Patients with iAMP21 tend to have a lower OS and EFS when compared to the other subgroups [1].

The United Kingdom ALL 97/99 studies reported a 5-year EFS of 29% and 5-year OS of 69% for 29 patients with iAMP21, and the Austrian and German ALL Berlin-Frankfurt-Munster (ALL-BFM) 86, 90, 95 and 2000 reported a 6-year EFS of 38% and OS of 66% for 29 iAMP21 patients. Both studies included very small number of patients and their treatment regiments were less intensive compared to the groups used later today [7,8]. The United Kingdom ALL 2003 studies reported 5-year EFS, relapse and OS were 78%, 16% and 89% respectively. The UK ALL 2003 showed better outcome as patients were allocated to the most intensive treatment arm (regimen C), which included augmented Berlin-Frankfurt-Munster consolidation, escalating Capizzi maintenance, double delayed intensification, and an option for first remission transplantation [8,9]. The main difference between regimen C and B were 8 additional doses of pegylated L-Asparaginase (PEG-Asp) and 2 courses of Capizzi interim maintenance with escalated doses of intravenous methotrexate [9]. The ALL-BFM 2000 trial used the same treatment regimen as ALL-BFM 86, 90 and 95 trials, but patients were not screened properly during the previous trials, patient numbers were small and biased. Hence, ALL-BFM 2000 was carried out with an 8-year long term follow up. The ALL-BFM 2000 showed better outcomes when compared to the previous ALL-BFM 86, 90 and 95 trials [10].

Harrison et al [12]. showed that iAMP21 and constitutional abnormalities involving chromosome 21. Interestingly, there were several patients with constitutional abnormalities involving chromosome 21 in the iAMP21 cohort. Harrison et al.[2] the 5 years EFS improved significantly from 50% to 70% when treated as high risk. The study by Suleimman Al-

Sweedan et al showed better 5-year EFS compared to the study of Moorman et al could be due to the median age difference. The median age in study by Suleimman Al Sweedan et al is 5.9 years compared to Moorman et al which is 9 years [11].

5. Conclusions

The records included in this study showed similar clinical characteristics. The prevalence was low as reported in all the studies. Patients were generally of older age and had a low WBC count [11]. The records showed different outcomes due to the difference in treatment regimen in each record. The limitation of this study is that it did not take to account other genetic abnormalities that can occur alongside with iAMP21.

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