Pediatr Pol 2024; 99 (4): 291-296
DOI: https://doi.org/10.5114/polp.2024.146417
Submitted: 11.06.2024, Accepted: 21.08.2024, Published: 30.12.2024

PEDIATRIA Polska
Polish Journal of PAEDIATRICS

ORIGINAL PAPER

# Incidence of secondary malignancies in Polish children treated for acute lymphoblastic leukemia according to the ALL-IC BFM 2002 protocol

Kamila Wypyszczak[1], Agata Pastorczak[2], Jerzy Kowalczyk[3], Tomasz Szczepański[4], Monika Lejman[5], Walentyna Balwierz[6], Bernarda Kazanowska[7], Katarzyna Derwich[8], Elżbieta Adamkiewicz-Drożyńska[9], Joanna Trelińska[10], Andrzej Kołtan[11], Maryna Krawczuk-Rybak[12], Tomasz Ociepa[13], Tomasz Urasiński[13], Grażyna Sobol-Milejska[14], Grażyna Karolczyk[15], Paweł Łaguna[16], Jan Styczyński[11], Jacek Wachowiak[8], Wojciech Młynarski[17]

[1]Department of Genetic Predisposition to Cancer, Medical University of Lodz, Poland
[2]Department of Genetic Predisposition to Cancer, Department of Pediatrics, Oncology and Hematology, Central Clinical Hospital, Lodz, Poland
[3]Department of Pediatric Hematology, Oncology and Transplantology, Medical University of Lublin, Poland
[4]Department of Pediatrics, Hematology and Oncology, Medical University of Zabrze, Zabrze, Poland
[5]Laboratory of Genetic Diagnostics, Medical University of Lublin, Lublin, Poland
[6]Department of Pediatric Oncology and Hematology, Children's University Hospital, Jagiellonian University, Krakow, Poland
[7]Department of Pediatric Transplantology, Oncology, Hematology, Medical University of Wroclaw, Wroclaw, Poland
[8]Department of Pediatric Oncology, Hematology and Transplantology, Medical University of Poznan, Poznan, Poland
[9]Department of Pediatrics, Hematology, Oncology and Endocrinology, Medical University of Gdansk, Gdansk, Poland
[10]Department of Pediatrics, Oncology and Hematology, Medical University of Lodz, Lodz, Poland
[11]Department of Pediatrics, Hematology and Oncology, Collegium Medicum of Bydgoszcz, Bydgoszcz, Poland
[12]Department of Pediatric Oncology, Hematology, Medical University of Bialystok, Bialystok, Poland
[13]Department of Pediatrics, Hemato-Oncology and Pediatric Gastroenterology, Medical University of Szczecin, Szczecin, Poland
[14]Department of Pediatrics, Medical University of Katowice, Katowice, Poland
[15]Department of Pediatric Oncology and Hematology, Children's Hospital, Kielce, Poland
[16]Department of Pediatric Oncology, Hematology, Clinical Transplantation and Pediatrics, Medical University of Warsaw, Warsaw, Poland
[17]Department of Pediatrics, Oncology and Hematology, Central Clinical Hospital, Lodz, Poland

## ABSTRACT

**Introduction:** Acute lymphoblastic leukemia (ALL) is the most commonly diagnosed childhood cancer, with a peak incidence around 5 years of age. Aim of the study was to assess the incidence, type, and outcome of secondary malignancies in children who were primarily treated for ALL.

**Material and methods:** We enrolled in the analysis 1868 children uniformly treated for ALL between 2 October 2002 and 22 December 2012 according to the protocol ALL-IC BFM 2002. In this study group, we assessed the incidence and type of secondary cancer and outcome.

**Results:** We identified 12 patients (0.64%) who developed secondary malignancies after the median time of 1.72 years from the primary diagnosis of ALL (range: 11.5 months to 18 years). The most frequently diagnosed second neoplasms were hematological malignancies (8 out of 12; 66.7%) including acute myeloid leukemia (AML) ($n = 4$), non-Hodgkin lymphoma (NHL) ($n = 2$), chronic myeloid leukemia (CML) ($n = 1$), and leukemia of unknown immunophenotype ($n = 1$). In total, four children developed subsequent solid tumors: Ewing sarcoma ($n = 1$), primitive neuroectodermal tumor ($n = 1$), myeloid sarcoma ($n = 1$), and solid tumors

**ADDRESS FOR CORRESPONDENCE:**

Kamila Wypyszczak, Department of Genetic Predisposition to Cancer, Medical University of Lodz, 4 Czechosłowacka St., 92-216 Lodz, Poland, e-mail: kamila.wypyszczak@umed.lodz.pl

of unknown origin ($n$ = 1). Children diagnosed with second cancer were non-significantly older at primary ALL diagnosis in comparison with patients without second cancer (12.083 [3.4–14.0] vs. 5.25 [3.2–10.2]; $p$ = 0.063). The risk group distribution differed between patients with and without a second cancer: 2 (16.67%) vs. 606 (32.65%) children were assigned to the standard risk (SR) group, 5 (41.67%) vs. 894 (48.17%) in the intermediate risk (IR) group, and 5 (41.67%) vs. 356 (19.18%) in the high risk (HR) group. Patients with secondary malignancies showed a significantly lower probability of 5-year overall survival as compared to children without subsequent tumors: 26.5% vs. 85.7%; $p < 10^{-5}$; HR = 5.9; 95% CI: 2.91–11.96.

**Conclusions:** Blood cancers are the most frequently observed malignancies in children treated for ALL during the first 3 years after treatment completion. Diagnosis of secondary tumor after being treated for ALL is related to poor outcome.

KEY WORDS:

**pediatric acute lymphoblastic leukemia, secondary neoplasm, ALL-IC BFM 2002.**

## INTRODUCTION

Acute lymphoblastic leukemia (ALL) is characterized by clonal proliferation of abnormal and immature cells of the lymphoid lineage. ALL is the most commonly diagnosed childhood cancer, with a peak incidence around 5 years of age. Approximately 220 cases of childhood ALL are diagnosed annually in Poland [1]. Treatment stratification, which is based on the biological features of leukemia and response to therapy, has contributed to the excellent 5-year probability of overall survival, exceeding 90% [2]. However, the development of a second cancer remains an important late complication affecting the outcome of childhood ALL [3].

The risk of second cancer in pediatric patients and young adults who have achieved complete remission in the course of ALL is about 3% at 15-year follow-up [4]. The earliest emerging second cancers are hematological malignancies, most commonly acute myeloid leukemia (AML). Brain tumors are the second most common type of secondary malignancy after ALL, occurring more than 7 years after the primary diagnosis [5].

Several factors increasing the risk of developing a second malignancy have been identified in pediatric patients treated for ALL. They include genetic predisposition, exposure to radiation, environmental factors, and exposure to chemotherapy using genotoxic drugs. Li Fraumeni syndrome (LFS) and inherited DNA repair disorders including ataxia-telangiectasia, Nijmegen breakage syndrome, Bloom's syndrome, and constitutional mismatch repair deficiency syndrome are particularly associated with the high risk of developing ALL and secondary malignancy [6–12]. The occurrence of secondary central nervous system (CNS) tumors is associated with the administration of radiation therapy during the ALL treatment [13]. These tumors are distinguished by a prolonged latency period following the initial diagnosis of ALL compared to secondary hematologic malignancy [14]. The administration of chemotherapeutic treatment may be related to the occurrence of a specific type of cancer. Application of alkylating agents or exposure to radiotherapy can lead to the development of secondary AML, diagnosed more than five years after the time of the original diagnosis. The use of topoisomerase II inhibitors can lead to the development of secondary AML, which is characterized by rearrangements involving the *KMT2A* gene, with a latency time of 2 years [15–17]. The use of methotrexate and 6-mercaptopurine during the maintenance phase, as well as increased doses of these drugs, may be associated with a higher risk of second cancers. In addition, polymorphisms within the thiopurine methyltransferase (*TPMT*) gene, which are associated with decreased activity of this enzyme, are also associated with an increased risk of developing a second malignancy [18].

The age of primary diagnosis may be a risk factor for secondary neoplasm development. The occurrence of ALL in patients older than 5 years of age is associated with a lower risk of developing a second cancer. Patients diagnosed with ALL before the age of five display an increased risk of CNS tumors, although this risk can be modified by previous radiotherapy treatment [19].

The purpose of this study was to assess the incidence and types of second cancers identified in a cohort of pediatric patients treated with the ALL-IC BFM 2002 protocol.

## MATERIAL AND METHODS

We retrospectively analyzed the clinical course of leukemia in children with newly diagnosed B-cell precursor acute lymphoblastic leukemia (BCP-ALL) with an age of 0–18 years treated in the 13 centers of the Polish Pediatric Leukemia/Lymphoma Study Group according to the ALL-IC BFM 2002. From October 2002 until December 2012, 1686 children were diagnosed with ALL. The clinical data for the study cohort were centrally gathered by the protocol coordinator. All the patients who were reported to the protocol coordinator were also included in the present study. The study was conducted in accordance with the Declaration of Helsinki.

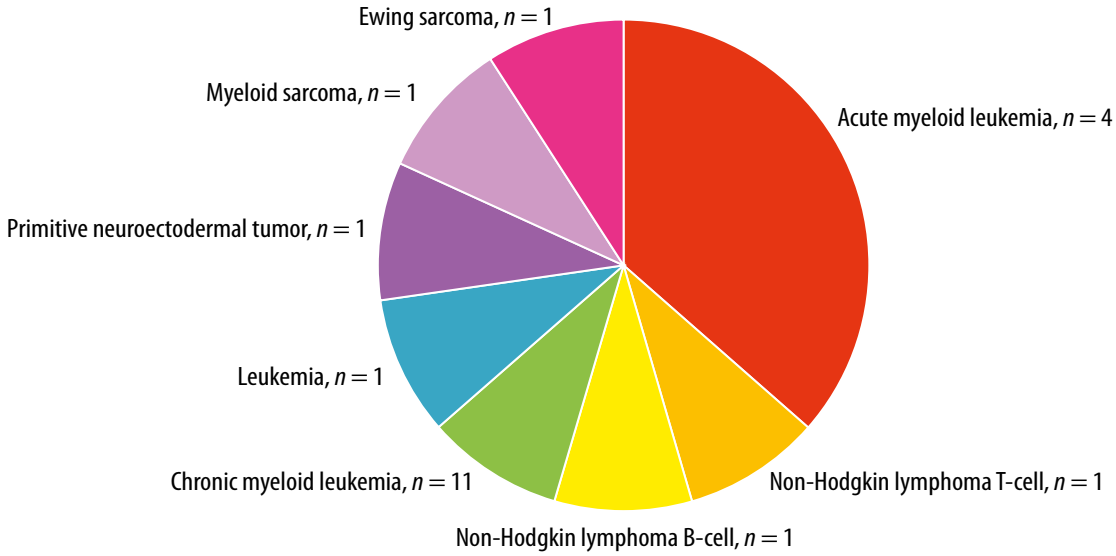


**FIGURE 1.** The incidence of secondary neoplasms among the 1868 patients treated due to acute lymphoblastic leukemia according to ALL-IC BFM 2002 protocol.

### STRATIFICATION INTO RISK GROUPS ACCORDING TO ALL IC-BFM 2002

Patients were stratified into risk groups according to the following criteria: standard risk group (SR) – age greater than 1 year and less than 6 years, white blood cells (WBC) < 20,000/μl and blast count/μl < 1,000 on day 8 of treatment; intermediate risk group (IR) – age greater than 1 year and less than 6 years and/or WBC > 20,000/μl and blast count/μl < 1000 on day 8 of treatment; high risk group (HR) – translocation t(9;22) [BCR/ABL] or t(4;11) [MLL/AF4] and blast count/μl > 1,000 on day 8 of treatment, M2 or M3 marrow on day 33 of treatment, M3 marrow on day 15 of treatment in IR group.

### STATISTICAL ANALYSIS

Differences in categorical variables were evaluated using the $\chi^2$ test or two-tailed Fisher's exact test. For continuous variables, the Mann-Whitney *U* test or Kruskal-Wallis nonparametric analysis of variance was used depending on the number of compared groups. Post-hoc comparisons were performed using Dunn's test if significance was ascertained in the Kruskal-Wallis test. Overall survival (OS) time was defined as the time from birth to the last follow-up. Patients still alive at the end of the study were treated as a censored observation. OS probabilities were compared using the log-rank test. Kaplan-Meier survival curves were used to represent probabilities of survival over time. This analysis was performed using GraphPad Prism 8 (GraphPad Software, San Diego, CA, USA).

## RESULTS

We identified 12 second neoplasms (0.64%) in the study cohort after the median time of 1.72 years from the primary diagnosis of ALL (range: 12.7 months to 3.4 years). In a cohort of 1868 patients, 234 (12.5%) died before the analysis, and 1634 (87.5%) were still alive. Median follow-up for the group was 4.3 years with a range of 2.2 to 6.8 years. Among patients with secondary neoplasm, 8 patients died (66.7%). Secondary malignancies occurred predominantly in ALL of B-cell origin ($n$ = 11/12) as compared to T-cell leukemia ($n$ = 1/12). The most frequently diagnosed second neoplasms were hematological malignancies (8 out of 12; 66.7%) including AML ($n$ = 4), non-Hodgkin lymphoma (NHL) ($n$ = 2), chronic myeloid leukemia ($n$ = 1), and leukemia of unknown immunophenotype ($n$ = 1). In total, 4 children developed subsequent solid tumors: Ewing sarcoma ($n$ = 1), peripheral primitive neuroectodermal tumor (PNET) ($n$ = 1), myeloid sarcoma ($n$ = 1), and unclassified solid tumor ($n$ = 1) (Figure 1). The latency period to secondary cancer diagnosis was 1.5 (1.2–1.8) years for hematological malignancies and 2.6 (2.3–3.0) years for solid tumors. The diagnosis of a second cancer was the first event after successful induction of remission in 10 out of these 12 patients. In the case of 5 patients, the cause of death was the progression of a second cancer. In one case, the patient died due to treatment-related toxicity. One patient received bone marrow transplantation from an unrelated donor and died because of graft-versus-host disease. Five patients who developed second cancer (granulocytic sarcoma, AML, B-cell non-Hodgkin's lymphoma [B-NHL], leukemia of unknown immunophenotype, and solid tumors of unknown origin) were primarily stratified into the high-risk group.

Patients who developed secondary malignancies showed a significantly lower probability of five-year overall survival as compared to children without second tumors (26.5% vs. 85.7%, respectively), $p < 10^{-5}$, HR = 5.91, 95% CI = 2.91–11.96 (Figure 2).

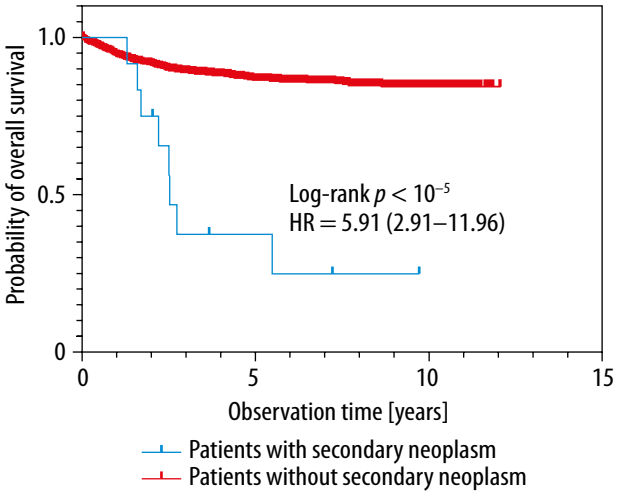


**FIGURE 2.** Kaplan-Meier curves presenting the comparison of overall survival among pediatric patients treated according to the ALL-IC BFM 2002 protocol depending on the incidence of secondary malignancies

We analyzed whether patients who developed second tumors differed from the remaining cohort with respect to WBC at ALL diagnosis, response to prednisone on day 8 of treatment, sex, age at diagnosis, and stratification into risk groups. Clinical characteristics are presented in Table 1. The median age of onset of ALL, although not statistically significant, showed a trend toward older age at primary diagnosis in the group of patients with secondary neoplasm. Five patients in whom a second cancer was diagnosed were stratified into the high-risk group. According to the protocol, assignment to the high-risk group or T-cell immunophenotype was associated with obligatory cranial radiotherapy of 12 Gy for all patients over 1 year of age. In this group, we identified a single case of B-NHL, AML, leukemia of unknown phenotype and granulocytic sarcoma.

## DISCUSSION

In the cohort of patients treated for ALL according to the ALL-IC BFM 2002 protocol, hematologic malignancies were the most common second cancers, with AML as the main type of tumor. Two patients developed NHL. Similar results were found in a group of patients from a German cohort treated for ALL between 1980 and 2014, where the most common secondary cancer occurring after ALL was AML. The second group consisted of CNS tumors and the third group of second cancers consisted

**TABLE 1.** Clinical characteristics of the study group depending on the occurrence of secondary malignancies

| Factor | | Clinical data | | *p*-value |
|---|---|---|---|---|
| | | Secondary neoplasm (*n* = 12) | No secondary neoplasm (*n* = 1674) | |
| WBC at diagnosis (N/μl) | | 8145 (3500–47450)* | 9500 (3800–33971) | 0.934 |
| Prednison response at day 8**, *n* | | | | |
| | Poor | 2 | 58 | 0.538 |
| | Good | 10 | 1616 | |
| | Data not available | | 39 | |
| Sex, *n* | | | | |
| | Male | 7 | 1050 | 0.902 |
| | Female | 5 | 806 | |
| Age, years | | 12,149 (3,430–14,062)* | 5,296 (3,193–10,158)* | 0.064 |
| Stratification to risk group, *n* (%) | | | | |
| | SR | 2 (17) | 606 (33) | 0.125 |
| | IR | 5 (42) | 894 (48) | |
| | HR | 5 (42) | 356 (19) | |
| Immunophenotype, B or T cell, *n* | | | | |
| | B | 11 | 1612 | 0.733 |
| | T | 1 | 209 | |
| | Data not available | | 35 | |
| Follow up, *n* (%) | | | | |
| | Death | 8 (67) | 226 (12) | < 0.05 |
| | Live | 4 (33) | 1630 (88) | |

**Median (Q1–Q3).*
***Calculates as poor when number of blast in perypheral blood was equal or greater then 1000.*
*HR – high risk group, IR – intermediate risk group, SR – standard risk group, WBC –*

of NHL [20]. In four of our patients, we observed the onset of AML with a median time of onset of 1.72 years, ranging from 1 to 2 years from primary diagnosis, which is consistent with previous observations [16]. The occurrence of secondary AML with a longer time from primary diagnosis may be caused by exposure to alkylating agents such as cyclophosphamide. The second group of drugs associated with an increased risk of secondary AML comprises topoisomerase II inhibitors. Usually this drug-induced AML harbors rearrangements at the 11q23 locus (involving the *KMT2A* gene) or monosomy of chromosome 5 and/or chromosome 8 in the leukemic karyotype. Very frequently there is a short interval between exposure to the drug and the development of AML [15, 21]. Two AML patients died because of AML progression. The occurrence of treatment-induced secondary AML has an unfavorable outcome, which can be partly explained by the presence of high-risk genetic abnormalities [22, 23]. Secondary tumors of CNS tumors are characterized by a longer latency period. Patients with second CNS tumors who were treated for ALL with radiation therapy show a shorter time to the occurrence of subsequent malignancy as compared to individuals who were not irradiated. At the same time, 89% of patients who developed brain tumors as a second tumor were treated with radiation therapy [14]. CNS cancers emerge as one of the most common second cancers in the Germline cohort, but the median follow-up of the study is nearly 10 years. Literature data indicate that the latency period between the occurrence of ALL and the occurrence of a second brain tumor is close to 10 years. However, the risk of secondary cancers as a result of radiotherapy is also related to the fractionated and cumulative dose [24]. One patient developed Ewing's sarcoma, which occurred during the maintenance phase of the protocol. The patient died due to the progression of the second tumor. The occurrence of Ewing's tumor as a second neoplasm in a cohort of patients treated for ALL is rare. Often the latency time from the initial diagnosis is longer than 4 years [25]. The incidence of PNET as a second cancer in a cohort of pediatric patients is extremely uncommon and associated with poor outcomes [26]. To date, few second PNETs have been identified in pediatric patients treated for ALL.

Genetic predisposition is a factor inextricably linked to the development of cancer. In one case, a germline pathogenic variant in the *TP53* gene was identified, which indicates a genetic predisposition to cancer as a main cause of subsequent tumors [27]. Fifty percent of patients diagnosed with the hypodiploid subtype of ALL carry a germline defect of the *TP53* gene which leads to the diagnosis of LFS [28]. This syndrome is associated with a high predisposition to sarcomas, breast cancer, and leukemia [6]. Among pediatric patients diagnosed with LFS and ALL, AML is often the second cancer. In our cohort, we identified 4 patients with second AML, but none of the patients presented with a hypodiploid karyotype in leukemic cells. However, several other DNA repair disorders including ataxia-telangiectasia and Nijmegen breakage syndrome are associated with a predisposition to cancer, most commonly T-cell leukemia and lymphoma [29, 30]. Germline defects involving the *ETV6* gene lead to the occurrence of thrombocytopenia type 5. It is now known that defects in this gene can strongly predispose to the occurrence of pediatric ALL, but also in a cohort of patients treated for ALL may be associated with a predisposition to second cancers such as AML or osteosarcoma [31]. We observed (non-significantly) higher median age at ALL diagnosis in the group of patients with secondary malignancies as compared to those without a subsequent tumor. In contrast, Bhatia *et al.* [32] reported an earlier age at ALL diagnosis among patients with a second cancer. However, this discrepancy may result from the short follow-up time, with a median time of observation of 4.3 years [32].

## LIMITATION OF THE STUDY

A limitation of the study is the relatively short follow-up time and the fact that patients over 18 years of age did not undergo further follow-up in outpatient clinics, which results in an underestimated number of second cancers. This is a particularly important limitation with respect to second brain tumors which develop as late complications (> 10 years from the primary diagnosis).

A significant percentage of patients who developed a second cancer were stratified into high-risk groups. This was caused by both rearrangements observed in tumor cells and steroid resistance. Patients classified in this group obtained more intensive treatment, which in combination with genetic factors may increase the risk of developing a second cancer [33].

## CONCLUSIONS

Blood cancers are the most frequently observed malignancies in children treated for ALL during the first 3 years after treatment completion. Diagnosis of a secondary tumor after being treated for ALL is related to a poor outcome.

## DISCLOSURES

1. Institutional review board statement: The study was approved by the Bioethical Committee of the Medical University of Lodz, approval number: RNN/183/10/KE.
2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

## REFERENCES

1. Kowalczyk JR, Balwierz W (eds.). Wprowadzenie do onkologii i hematologii dziecięcej: skrypt dla lekarzy specjalizujących się

w onkologii i hematologii dziecięcej. Warszawa: Centrum Medyczne Kształcenia Podyplomowego; 2011.
2. Inaba H, Greaves M, Mullighan CG. Acute lymphoblastic leukaemia. Lancet 2013; 381: 1943-1955.
3. Robison LL. Late effects of acute lymphoblastic leukemia therapy in patients diagnosed at 0-20 years of age. Hematology Am Soc Hematol Educ Program 2011; 2011: 238-242. DOI: 10.1182/ASHEDUCATION-2011.1.238.
4. Hijiya N, Hudson MM, Lensing S, et al. Cumulative incidence of secondary neoplasms as a first event after childhood acute lymphoblastic leukemia. JAMA 2007; 297: 1207-1215.
5. Bhatia S, Sklar C. Second cancers in survivors of childhood cancer. Nat Rev Cancer 2002; 2: 124-132.
6. Hendrickson PG, Luo Y, Kohlmann W, et al. Radiation therapy and secondary malignancy in Li-Fraumeni syndrome: a hereditary cancer registry study. Cancer Med 2020; 9: 7954-7963.
7. Bielorai B, Fisher T, Waldman D, et al. Acute lymphoblastic leukemia in early childhood as the presenting sign of ataxia-telangiectasia variant. Pediatr Hematol Oncol 2013; 30: 574-582.
8. Schoenaker MHD, Suarez F, Szczepanski T, et al. Treatment of acute leukemia in children with ataxia telangiectasia (A-T). Eur J Med Genet 2016; 59: 641-646.
9. Pastorczak A, Stolarska M, Trelińska J, et al. Nijmegen breakage syndrome (NBS) as a risk factor for CNS involvement in childhood acute lymphoblastic leukemia. Pediatr Blood Cancer 2011; 57: 160-162.
10. Adams M, Jenney M, Lazarou L, et al. Acute myeloid leukaemia after treatment for acute lymphoblastic leukaemia in girl with Bloom syndrome. J Genet Syndr Gene Ther 2013; 4: 1000177. DOI: 10.4172/2157-7412.1000177.
11. Ripperger T, Schlegelberger B. Acute lymphoblastic leukemia and lymphoma in the context of constitutional mismatch repair deficiency syndrome. Eur J Med Genet 2016; 59: 133-142.
12. Cao J, Tan RYC, Li ST, et al., Identifying ataxia-telangiectasia in cancer patients: Novel insights from an interesting case and review of literature. Clin Case Rep 2020; 9: 995-1009.
13. Relling MV, Rubnitz JE, Rivera GK, et al. High incidence of secondary brain tumours after radiotherapy and antimetabolites. Lancet 1999; 354: 34-39.
14. Schmiegelow K, Levinsen MF, Attarbaschi A, et al. Second malignant neoplasms after treatment of childhood acute lymphoblastic leukemia. J Clin Oncol 2013; 31: 2469-2476.
15. Sandoval C, Pui CH, Bowman LC, et al. Secondary acute myeloid leukemia in children previously treated with alkylating agents, intercalating topoisomerase II inhibitors, and irradiation. J Clin Oncol 1993; 11: 1039-1045.
16. Wang X, Ding D, Liu Y. Acute myeloid leukemia secondary to acute B lymphoblastic leukemia treated with maintenance therapy in a child: a case report. Cancer Rep (Hoboken) 2022; 5: e1717. DOI: 10.1002/CNR2.1717.
17. Higgins A, Shah MV. Genetic and genomic landscape of secondary and therapy-related acute myeloid leukemia. Genes 2020; 11: 749. DOI: 10.3390/GENES11070749.
18. Schmiegelow K, Nielsen SN, Frandsen TL, Nersting J. Mercaptopurine/methotrexate maintenance therapy of childhood acute lymphoblastic leukemia: clinical facts and fiction. J Pediatr Hematol Oncol 2014; 36: 503. DOI: 10.1097/MPH.0000000000000206.
19. Neglia JP, Meadows AT, Robison LL, et al. Second neoplasms after acute lymphoblastic leukemia in childhood. N Engl J Med 1991; 325: 1330-1336.
20. Scholz-Kreisel P, Kaatsch P, Spix C, et al. Second malignancies following childhood cancer treatment in Germany from 1980 to 2014. Dtsch Arztebl Int 2018; 115: 385-392.
21. Szotkowski T, Rohon P, Zapletalova J, et al. Secondary acute myeloid leukemia – a single center experience. Neoplasma 2010; 57: 170-178.
22. Strickland SA, Vey N. Diagnosis and treatment of therapy-related acute myeloid leukemia. Crit Rev Oncol Hematol 2022; 171: 103607. DOI: 10.1016/J.CRITREVONC.2022.103607.
23. Fianchi L, Pagano L, Piciocchi A, et al. Characteristics and outcome of therapy-related myeloid neoplasms: Report from the Italian network on secondary leukemias. Am J Hematol 2015; 90: E80-E85. DOI: 10.1002/AJH.23966.
24. Dracham CB, Shankar A, Madan R. Radiation induced secondary malignancies: a review article. Radiat Oncol J 2018; 36: 85-94.
25. Wolpert F, Grotzer MA, Niggli F, et al. Ewing's sarcoma as a second malignancy in long-term survivors of childhood hematologic malignancies. Sarcoma 2016; 2016: 5043640. DOI: 10.1155/2016/5043640.
26. Khadwal A, Biswas G, Arora B, et al. Primitive neuroectodermal tumor (PNET) as second malignancy after treatment of Hodgkin's disease. Indian J Pediatr 2006; 73: 437-438.
27. Suarez CR, Bertolone SJ, Raj AB, Coventry S. Second malignant neoplasms in childhood acute lymphoblastic leukemia: primitive neuroectodermal tumor of the chest wall with germline p53 mutation as a second malignant neoplasm. Am J Hematol 2004; 76: 52-56.
28. Al-Mahayri ZN, AlAhmad MM, Ali BR. Long-term effects of pediatric acute lymphoblastic leukemia chemotherapy: can recent findings inform old strategies? Front Oncol 2021; 11: 710163. DOI: 10.3389/FONC.2021.710163/BIBTEX.
29. Bakhtiar S, et al. The incidence and type of cancer in patients with ataxia-telangiectasia via a retrospective single-centre study. Br J Haematol 2021; 194: 879-887.
30. El Hasbaoui B, Elyajouri A, Abilkassem R, Agadr A. Nijmegen breakage syndrome: case report and review of literature. Pan Afr Med J 2020; 35: 85. DOI: 10.11604/PAMJ.2020.35.85.14746.
31. Junk SV, Klein N, Schreek S, et al. TP53, ETV6 and RUNX1 germline variants in a case series of patients developing secondary neoplasms after treatment for childhood acute lymphoblastic leukemia. Haematologica 2019; 104: e402-e405. DOI: 10.3324/HAEMATOL.2018.205849.
32. Bhatia S, Sather HN, Pabustan OB, et al. Low incidence of second neoplasms among children diagnosed with acute lymphoblastic leukemia after 1983. Blood 2002; 99: 4257-4264.
33. DelRocco NJ, Loh ML, Borowitz MJ, et al. Enhanced risk stratification for children and young adults with B-cell acute lymphoblastic leukemia: a Children's Oncology Group Report. Leukemia 2024; 38: 720-728.