A report on second neo-plasms in seven children with solid tumors

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OBJECTIVE: *This study aims to investigate the characteristics and related high risk factors of second neoplasms after chemotherapy and radiotherapy in children with solid tumors.*
METHODS: *The detailed clinical data of seven children with malignant solid tumors, who were treated in our department, were retrospectively analyzed, in order to summarize the clinical characteristics of the secondary onset of second neoplasms, and determined the risk factors related to the occurrence of second neoplasms. RESULTS: (1) Clinical characteristics: Among the seven children with malignant solid tumors, three children had rhabdomyosarcoma (3/132, 2.27%), two children had hepatoblastoma (2/313, 0.64%), one child had neuroblastoma (1/305, 0.33%), and one child had inflammatory myofibroblastoma (1/3, 33.33%). Furthermore, among these children, four children were boys and three children were girls, and their onset age ranged within 5-34 months, with a median onset age of 27 months. Moreover, among these children, three children were ≤1 year old. All second neoplasms exhibited symptoms, and the diagnosis was made after the complete remission of the first primary tumor. The time interval between these two tumors was within 17-78 months, and the median time was 38 months. Three of seven children with rhabdomyosarcoma were treated with chemotherapy in combination with radiotherapy, while four children only received the chemotherapy. The chemotherapy cycles were 6-39 times, and the median chemotherapy cycles were 10 times. Among these children, one child with relapsed stage IV rhabdomyosarcoma and one child with stage IV retroperitoneal neuroblastoma had 39 cycles and 33 cycles of chemotherapy respectively. (2) Characteristics of the accumulated doses of high-risk chemotherapy drugs: The accumulated dose of cyclophosphamide in six patients was within 2.47-44.45 g/m^2, with a median of 6.14 g/m^2. The accumulated dose of ifosfamide in five patients was within 13.63-96.41 mg/m^2, with a median of 31.23g/m^2. The accumulated dose of etoposide in six patients was within 1,237.35-3,754.95 mg/m^2, with a median of 1,548.67 mg/m^2. The accumulated dose of anthracyclines in seven patients was within 150.68-843.78 mg/m^2, with a median of 329.73 mg/m^2. The accumulated dose of vincristine in seven patients was within 3.11-18.89 mg/m^2, with a median of 15.92 mg/m^2. The accumulated dose of cisplatin in seven patients was within 271.23-1,681.59 mg/m^2, with a median of 733.07 mg/m^2. Children with abdominal inflammatory myofibroblastic tumors did not apply cyclophosphamide, ifosfamide and etoposide regimens. The main chemotherapy drugs consisted of methotrexate, pirarubicin, cisplatin and vincristine. (3) Radiotherapy doses. (4) Characteristics of second neoplasms: Among the seven children with second neoplasms, five children had leukemia, 3 patients with rhabdomyosarcoma were combined with radiotherapy. The doses of radiation were 40 and 45GY" after "(3) Radiotherapy doses (four children had acute myeloid leukemia and one children had acute B-lymphoblastic leukemia), one child had myelodysplastic syndrome, and one child had myeloid sarcoma. Furthermore, among these seven children, four children (4/7) had abnormal chromosomes, two children were normal, and one child gave up the treatment and underwent the chromosome test after the diagnosis of second neoplasms.*
CONCLUSION: *The incidence of secondary onset of second neoplasms in children with malignant solid tumors is not high, considering that this is correlated to the use of alkylating agents, topoisomerase II inhibitors, platinum-based chemotherapy drugs and radiotherapy, and associated with the chromosomal abnormalities of children.*

KEY WORDS: Chemotherapy, Children, Radiotherapy, Second malignant neoplasm, Solid tumor

Introduction

In recent years, the prognosis of childhood tumors has significantly improved, and the number of long-term survivors has increased, which was mainly due to the

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improvement of multidisciplinary treatment, including advances in neoadjuvant chemotherapy, radiotherapy and surgery. As the number of long-term disease-free survival children increased, the occurrence of potential treatment-related side effects (e.g. second malignant neoplasms) has brought about new problems. Second malignant neoplasms refer to malignancies with different histological origins that occur at least two months after the end of the primary cancer treatment. The occurrence of second malignant neoplasms is mainly due to genetic factors, and caused by the chemotherapy and/or radiotherapy for the first primary tumor [1].

With the gradual increase in children undergoing chemotherapy-radiotherapy and the prolonged long-term disease-free survival time, the adverse reactions of chemotherapy-radiotherapy have gradually emerged. One of the long-term adverse reactions is that it can induce second neoplasms, and the more common second neoplasm is acute non-lymphoblastic leukemia. It has been reported that 8%-12% of patients would have second primary neoplasms within 20 years from the initial diagnosis of the malignant tumor [2]. Furthermore, studies have found that second malignant neoplasms (SMNs) are the most serious tumor complications in childhood cancer survivors [3-6].

The major tumor studies on second neoplasms have mainly focused on hematological tumors and brain tumors, while studies have rarely reported on the risk of second neoplasms for rare childhood tumors [7,8]. The study results for second neoplasms with a large sample in 13 registration centers revealed that among the 10,988 enrolled children, 175 children had second neoplasms, and the standardized incidence ratio (SIRS) of second neoplasms was 4.6, with a 95% confidence interval (CI: 3.9-5.3). Furthermore, the incidence of second neoplasms in liver tumors was 0.27% (1/367), the incidence of second neoplasms in soft tissue sarcoma was 1.40% (30/2143), and the incidence of second neoplasms in retinoblastoma was 3.41% (45/1321). The proportion of second neoplasms that occur within one year after the diagnosis of the primary tumor was 0.45% (10/2210) and 1.05 % (24/2276) within 1-4 years. The cumulative incidence rate of second malignant neoplasms at 10 years after the onset of the first neoplasm in non-central nervous system tumor survivors is eight times higher than that of the general population. Furthermore, among children who have survived, the risk of new malignant neoplasms would significantly increase, even in the early years of the diagnosis of primary tumors [9]. For chemotherapy, alkylating agents, etoposide and anthracyclines have been well-documented for increased risk of acute myeloid leukemia within 10 years after the treatment of childhood cancer [10].

The role of chemotherapy in the etiology of solid tumors remains unknown, but alkylating agents and anthracyclines are associated with increased risk of subsequent sarcoma [10]. A recent study on survivors with unirradiated childhood cancer revealed their drug-dose dependence, especially after the treatment of childhood sarcoma and leukemia. These two types of drugs have resulted in an increase in risk of breast cancer [11]. In addition, radiotherapy is also a risk factor for increased risk of occurrence of second neoplasms [12]. Due to the low incidence of non-central nervous system tumors in children, the characteristics in occurrence of second neoplasms have rarely been reported. Three cases of soft tissue sarcoma, two cases of hepatoblastoma, one case of neuroblastoma and one case of inflammatory myofibroblastoma were reported among seven children with the primary tumors in the present study, and these were mainly uncommon children non-central nervous system solid tumors. In addition, the onset of these children was young, but they were all confirmed with second neoplasms. The characteristics of the disease and the risk factors of second neoplasms are presently reported to provide guidance for pediatric oncologists in clinical treatment.

Methods

The clinical data of seven children with malignant solid tumors were collected. These children were confirmed with second neoplasms after receiving treatment in the department of our hospital from June 1, 2006 to December 2017, and achieving complete remission. The treatment of primary tumors and the diagnosis of second neoplasms of these children were retrospectively analyzed.

The relatives were informed with all clinical treatments and examinations for these children, and provided signed informed consent. The present study was approved by the Ethics Committee of Beijing Tongren Hospital, Capital Medical University. The ethics number is 2014-1102 in Beijing Tongren Hospital. The immunotype of the bone marrow and chromosome karyotype of the peripheral blood were sent to Beijing Hightrust Diagnostics for testing.

The primary tumors of seven children were all malignant solid tumors, and all of these were clearly diagnosed by operation and pathology. Chemotherapy and radiotherapy were given to these children, according to international solutions, after completing the whole body examination and clearing the stages. For recurrent cases, a combined therapy with targeted drugs was given, and the primary tumors achieved complete remission. The complete remission time was more than two months. The study for all second neoplasms reported in this group of patients were carried out in accordance with the diagnostic criteria and grouping in the third edition of the International Classification of Childhood Cancer [13]. All seven patients were diagnosed with second neoplasms.

The SPSS 21.0 software was used for the data analysis, and $P<0.05$ was considered statistically significant.

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Results

For the clinical characteristics: three children had rhabdomyosarcoma (3/132, 2.27%), two children had hepatoblastoma (2/313, 0.64%), one child had neuroblastoma (1/305, 0.33%), and one child had inflammatory myofibroblastoma (1/3, 33.33%). Among these children, four children were boys and three children were girls, and their onset age for first neoplasms ranged within 5-34 months, with a median onset age of 27 months. Furthermore, among these children, three children were ≤1 years old. All second neoplasms exhibited symptoms, and the diagnosis was made after the complete remission of the first primary tumor. The time interval between these two tumors was within 17-78 months, and the median time was 38 months. Among these seven children, three children with rhabdomyosarcoma were treated with chemotherapy in combination with radiotherapy, while four children only received chemotherapy. The chemotherapy cycles were 6-39 times, and the median chemotherapy cycles were 10 times. Among these children, one child had relapsed stage IV rhabdomyosarcoma, while one child had stage IV retroperitoneal neuroblastoma, and these children received 39 and 33 cycles of chemotherapy, respectively. The primary tumors and second neoplasms of these seven children are presented in Table I.

The characteristics of the accumulated dose of high-risk chemotherapy drugs The accumulated dose of ifosfamide in five patients was within 13.63-96.41 mg/m^2, with a median of 31.23 g/m^2. The accumulated dose of etoposide in six patients was within 1,237.35-3,754.95 mg/m^2, with a median of 1,548.67 mg/m^2. The accumulated dose of anthracyclines in seven patients was within 150.68-843.78 mg/m^2, with a median of 329.73 mg/m^2. The accumulated dose of vincristine in seven patients was within 3.11-18.89 mg/m^2, with a median of 15.92mg/m^2. The accumulated dose of cisplatin was within 271.23-1,681.59 mg/m^2, with a median of 733.07 mg/m^2. Children with abdominal inflammatory myofibroblastic tumors did not receive the cyclophosphamide, ifosfamide and etoposide regimens. The main chemotherapy drugs consisted of methotrexate, pirarubicin, cisplatin and vincristine.

Radiotherapy dose: One patient received external mediastinal radiotherapy (the prophylactic radiotherapy in the whole lung for the first time, with a dose of 12 GY, and 28 GY for the total pulmonary and mediastinal radiotherapy after recurrence), with a total dose of 40 GY.

Characteristics of the second neoplasms: For the types of these seven second primary tumors, four children had acute myeloid leukemia, one children had acute B-lymphoblastic leukemia, one child had myelodysplastic syndrome, and one child had myeloid sarcoma.

Furthermore, among these seven children, four children who underwent a routine chromosome test had abnormal chromosomes, two children were normal, and one child was diagnosed with leukemia, who gave up the treatment and did not undergo the test for chromosomes. The details of the dose for the high-risk chemotherapy drugs, radiotherapy and chromosome test of these seven children are presented in Table II.

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TABLE I - *Clinical characteristics of second neoplasms in children with solid tumor*

Case	Age of onset (months)	Type of Primary tumor	Primary stage	CR duration (months)	Type of Second tumor	The time interval between the two tumors (months)
1	12	Left orbital rhabdomyosarcoma	Stage III	24	Acute Myeloblastic Leukemia Partially Differentiated-M2	73
2	27	Right orbital rhabdomyosarcoma	StageIII	29	Myeloid sarcoma	38
3	5	Left dorsal rhabdomyosarcoma	StageIV (Lung and lymph node metastasis)	15	Acute unicellular leukemia	78
4	34	Retroperitoneal neuroblastoma	StageIV (Bone marrow metastasis)	3	B-cell acute lymphoblastic leukemia	48
5	8	Abdominal inflammatory myofibroblastoma	Stage III	6	Acute promyelocytic Acute Myeloblastic Leukemia Partially Differentiated-M2	18
6	31	Hepatoblastoma	Stage III	9	Acute myelomonocytic leukemia	17
7	27	Hepatoblastoma	Stage IV	36	Myelodysplastic syndrome	13

CR: complete response.

TABLE II - *The characteristics of high risk chemotherapy drug dose, radiotherapy and chromosome karyotype in 7 children*

Case	Number of chemotherapy cycles per tumor	Cumulative cyclophosphamide dose(g/m^2)	Accumulated dose of Ifosfamide (g/m^2)	Cumulative dose of anthracycline (mg/m^2)	Cumulative etoposide dose (mg/m^2)	Cisplatin cumulative dose (mg/m^2)	Radiotherapy	Chromosome abnormalities
1	6	2.72	13.63	154.55	1500	272.75	45Gy (orbit)	Yes
2	6	2.47	21.23	150.68	1565	271.23	45Gy (orbit)	No
3	39	8.29	96.41	225.41	2867.4	1485.18	40GY (whole lung and mediastinal radiotherapy)	Yes
4	33	44.45	/3.42	329.73	3754.95	980.18	No	Yes
5	10	-	-	592.77	-	731.33	No	Unidentified
6	10	3.99	-	571.98	1237.35	733.07	No	No
7	24	9.53	14.23	843.78	1532.34	1681.59	No	Yes

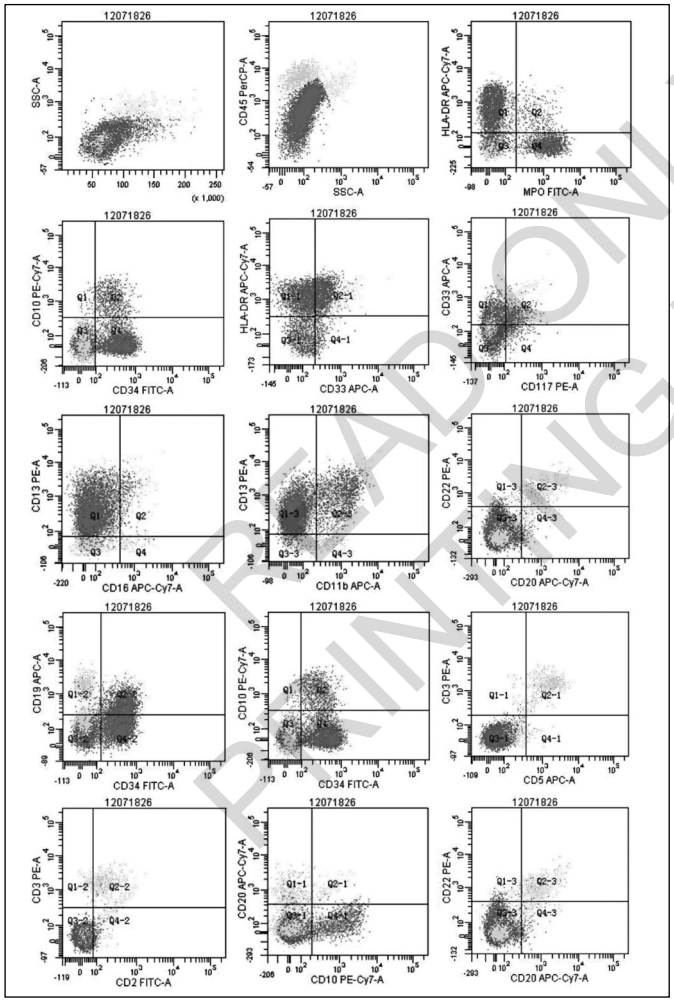

Fig. 1: Characteristics of the acute myeloid leukemia type M2 in Case 1: Abnormal cells accounted for 90.1%, and all expressed CD13, and partially expressed HLA-DR, CD19, CD33, CD34, MPO. However, the relative specific antigen CD10, CD19, CD20, CD2, CD3 of acute lymphoblastic leukemia were not significantly expressed.

CASE N. 1

The results of the bone marrow flow cytometry for second neoplasms with a diagnosis of leukemia are shown in Fig. 1, and the test results for abnormal chromosomes are presented in Fig. 2.

CASE N. 2

The primary tumor was rhabdomyosarcoma, and the second neoplasm was myeloid sarcoma after healing. The pathological features of the primary tumor and second neoplasm are presented in Fig. 3.

Discussion

In pediatric patients, modern radiotherapy in combination with new chemotherapy can significantly improve the survival of children with hematological diseases and solid tumors. However, approximately 40%-70% of cancer patients may have disease-associated or treatment-associated diseases [14]. Furthermore, the risk of second neoplasms is significantly higher than that of the general population, which range within 3-10 times of that of the general population [15,16]. A total of 13,107 children with childhood tumors, who were under 15 years old and has a long-term survival, were investigated in North America and Canada, and the study findings for second neoplasms revealed that 190 (0.1%) children with non-central nervous system tumors (including neuroblastoma, nephroblastoma, rhabdomyosarcoma, retinoblastoma and hepatoblastoma) developed second neoplasms. The second most common neoplasms are osteoarticular cancer (*n*=36), followed by leukemia (*n*=31), soft tissue sarcoma (including the heart, *n*=18) and thyroid cancer

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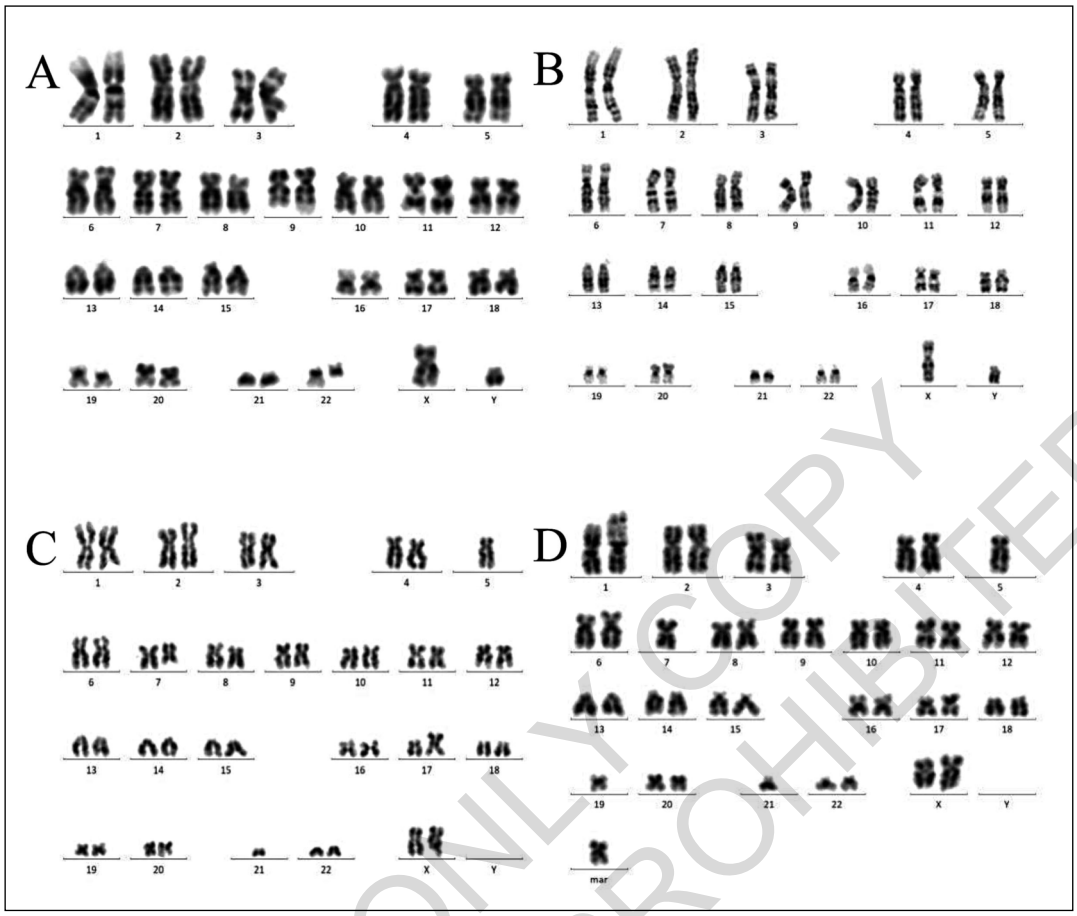

Fig. 2: Chromosome images
A represents the abnormal chromosome images of Case 1 (46, XY, t (9;22) (q34,q11)[20]):
B represents the normal chromosomal image of Case 2;
C represents the abnormal chromosome karyotype image of Case 3 (41-45,XX,der(5;17)(p10; q10), del(7)(q22)[cp13]/43, idem, add(11)(q23), add(18)(q23).-19,-21[1]/46,XX[1]);
D represents the abnormal chromosome karyotype image of Case 7 (43,XX,add(1)(p22),del(3)(p21),-5,-7,der(17;21)(q10;q10), 19,+mar[13]/45,XX,-5,add(17)(p11)[2]/46,XX[5]).

(*n*=16). The standardized incidence of second neoplasms in different tumors was the highest [12] in rhabdomyosarcoma, followed by hepatoblastoma (5.6), while nephroblastoma was on third place (3.1). The standardized incidence of second neoplasms at different diagnostic ages of first neoplasms is as follows: <1 year old is 7, 1-4 years old is 5.8, 5-9 years old is 7.0, and 10-14 years old is 7.1. The standardized incidence of second neoplasms after the first neoplasm was the lowest in children within 1-4 years old. The standardized incidence of second neoplasms at different follow-up periods was as follows: <1 year old is 53, 1-5 years old is 25, and 5-10 years old is 17. As the follow-up time is extended, the standardized incidence decreases. The risk of second neoplasms that result from the first neoplasm was the highest in children <1 year old [17]. Among the seven children in the present study, three children (3/7, 42.86%) had an onset age of ≤1 years old and three children's had rhabdomyosarcoma (3/7, 42.86%), which is in line with the literature reports. However, the follow-up time was >1 year in this group of children, which is not consistent with the highest risk of second neoplasms within one year. In addition, the characteristics of two tumors revealed that leukemia is the most common (5/7, 71.43%), while myelodysplastic syndrome and myeloid sarcoma were each identified in one child.

With respect to the risk factors for second neoplasms in children with tumors, it is clear that chemotherapy and radiotherapy should be considered. The analysis of risk factors associated with the occurrence of second neoplasms after an average follow-up period of 20.7 years for a total of 6,165 children with long-term cancer, who survived for over five years, revealed that the use of anthracycline is the main risk factor for breast cancer, and is associated with an accumulated dose (>250 mg/m^2. Although no chemotherapy was given, the standardized tumor incidence was 3.6). Systemic radiotherapy and pulmonary and mediastinal radiotherapy are high risk factors for breast cancer in women. Cyclophosphamide is a main risk factor for sarcoma,

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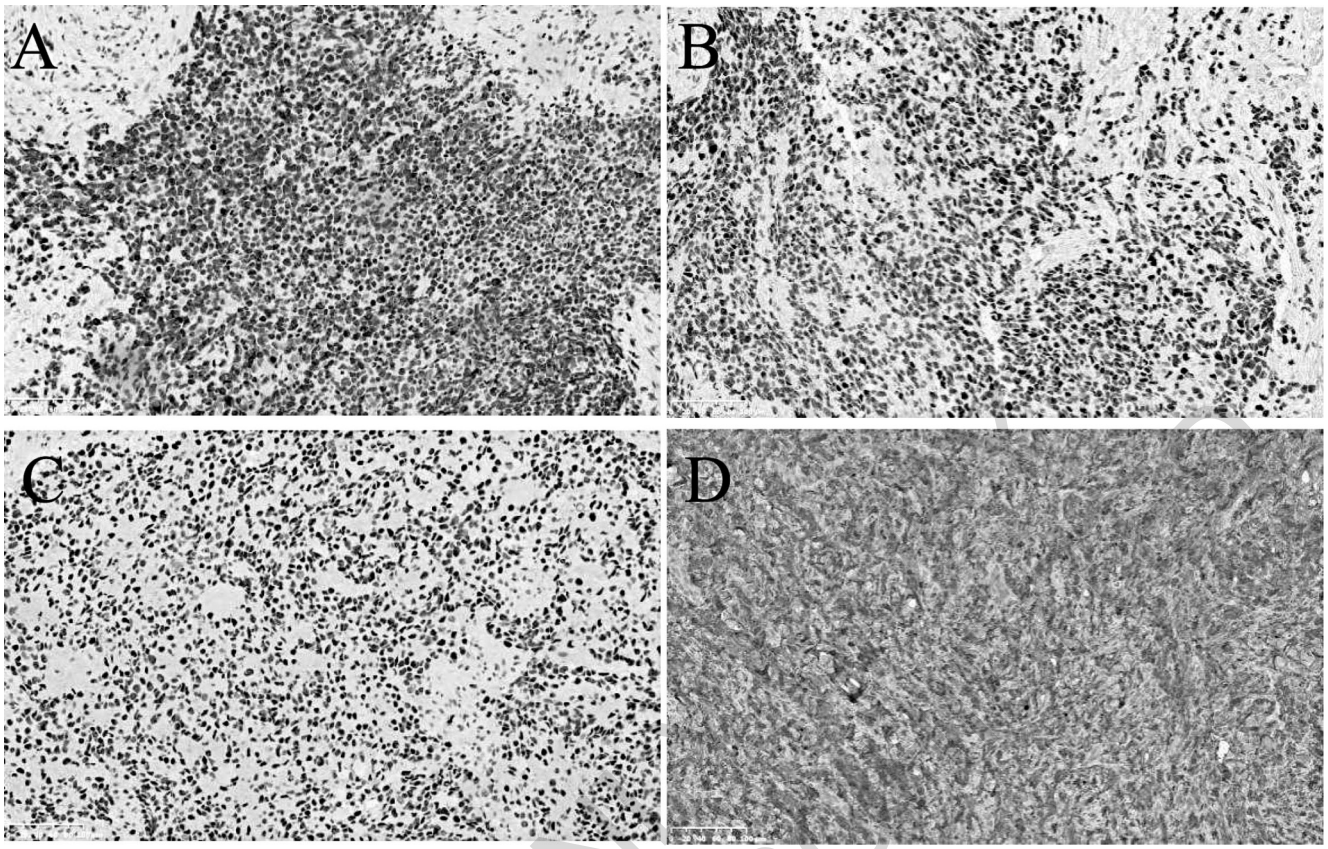

Fig. 3: A-C presents the pathological results for the rhabdomyosarcoma (primary tumor) in Case 2:
A represents Desmin+ (×100); B represents MyoD1+ (×100); C represents Myognen+ (×100); D represents the pathological results for the secondary neoplasms in Case 2, MPO+ (×100).

which is associated with an accumulated dose. Both cyclophosphamide and ifosfamide are the main risk factors of osteosarcoma, but these not associated with the accumulated dose [16]. In addition, a study suggested that etoposide of >4,000 mg/m^2 would increase the risk of tumorigenesis by four times [18]. For adult ovarian cancers, studies on platinum-based chemotherapy regimens and the risk of leukemia suggest that the standardized incidence of platinum-induced second neoplasms is 6.5 for carboplatin and 3.3 for cisplatin [19]. All seven patients reported in the present study were given chemotherapy. Among the seven patients treated with anthracyclines, four patients had an accumulated dose of >250 mg/m^2. Furthermore, six patients received etoposide, and cyclophosphamide and/or ifosfamide. The combination of three drugs that commonly induced second neoplasm was the most important factor for the occurrence of second neoplasms. One child with inflammatory myofibroblastoma only received anthracyclines, but the accumulated dose was >500 mg/m^2, and the onset age was <1 years old, which increased the risk of second neoplasms.

A nested case-control study revealed that any exposure to ionizing radiation is a risk factor for the secondary onset of second neoplasms, especially sarcoma. When the irradiation dose increases to more than 50 Gy from 10.0-29.9 Gy, the risk coefficient would increase to 114.1 from 15.6 [11]. Therefore, radiotherapy is a well-defined risk factor for the occurrence of second neoplasms. However, a change in radiotherapy is needed to reduce the occurrence of second neoplasms [1,12,20]. Three patients with rhabdomyosarcoma were treated with radiotherapy, which increased the risk of second neoplasms.

The third clear reasons for the occurrence of second neoplasms are genetic factors and cancer tendency syndrome. RB1, RCA1/2, NF1, TP53 and other genes are high risk factors for the occurrence of second neoplasms. Some of these are treatment-related gene abnormalities, while most of these occur within 2-3 years after etoposide treatment and 5-7 years after alkylation agent treatment [20]. In the present study, seven children with solid tumors developed second neoplasms within an average of 38 months after 17-78 months of cure. Four of these chidren had abnormal chromosomes, who could not be excluded completely from the treatment-related chromosomal abnormalities. Therefore, it is recommended that children with tumors should routinely carry out a chromosome test and related tumor gene detection modalities.

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Conclusion

In summary, children with solid tumors should avoid using high-risk chemotherapy drugs and an unsafe cumulative dose during treatment, because these drugs may lead to second neoplasms. Furthermore, routine dynamic follow-ups should be carried out to early detect these second neoplasms, and allow these patients to be treated in a timely manner, even after complete remission of the primary tumors.

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Riassunto

Questo studio ha lo scopo di studiare le caratteristiche e i relativi fattori ad alto rischio delle seconde neoplasie dopo chemioterapia e radioterapia nei bambini con tumori solidi.
Sono stati analizzati retrospettivamente e dettagliatamente i dati clinici di sette bambini con tumori solidi maligni, che sono stati trattati nel nostro reparto, al fine di riassumere le caratteristiche cliniche all'inizio dell'insorgenza delle seconde neoplasie e determinare i fattori di rischio correlati al verificarsi di questa insorgenza.
Caratteristiche cliniche: tra i sette bambini con tumori solidi maligni, tre bambini avevano rabdomiosarcoma (3/132, 2,27%), due bambini avevano epatoblastoma (2/313, 0,64%), un bambino aveva neuroblastoma (1/305, 0,33%) e un bambino presentava miofibroblastoma infiammatorio (1/3, 33,33%). Inoltre si trattava di quattro bambini e tre bambine, e la loro epoca di insorgenza era compresa tra 5-34 mesi, con una mediana di 27 mesi; tre bambini avevano età non superiore ad 1 anno.
Tutte le seconde neoplasie erano sintomatiche e la diagnosi era stata fatta dopo la completa remissione del primo tumore primario. L'intervallo di tempo tra questi due tumori era compreso tra 17 e 78 mesi e il tempo mediano era di 38 mesi. Tre su sette bambini con rabdomiosarcoma sono stati trattati con chemioterapia in combinazione con radioterapia, mentre quattro bambini hanno ricevuto solo la chemioterapia. I cicli di chemioterapia erano ripetuti da 6 a 39 volte e i cicli di chemioterapia in media 10 volte. Un bambino con rabdomiosarcoma in stadio IV recidivo e un bambino con neuroblastoma retroperitoneale in stadio IV hanno avuto rispettivamente 39 cicli e 33 cicli di chemioterapia.
Caratteristiche delle dosi accumulate di farmaci chemioterapici ad alto rischio: la dose accumulata di ciclofosfamide in sei pazienti era compresa tra 2,47 e 44,45 g/m^2, con una mediana di 6,14 g/m^2. La dose accumulata di ifosfamide in cinque pazienti era compresa tra 13,63 e 96,41 mg/m^2, con una mediana di 31,23 g/m^2. La dose accumulata di etoposide in sei pazienti era compresa tra 1.237,35-3.754,95 mg/m^2, con una mediana di 1.548,67 mg/m^2. La dose accumulata di antracicline in sette pazienti era compresa tra 150,68-843,78 mg/m^2, con una mediana di 329,73 mg/m^2. La dose accumulata di leurocristina in sette pazienti era compresa tra 3,11 e 18,89 mg/m^2, con una mediana di 15,92 mg/m^2. La dose accumulata di cisplatino in sette pazienti era compresa tra 271,23-1,681,59 mg/m^2, con una mediana di 733,07 mg/m^2.
I bambini con tumori miofibroblastici infiammatori addominali non hanno ricevuto regimi di ciclofosfamide, ifosfamide ed etoposide. I principali farmaci chemioterapici sono stati il metotrexato, la pirarubicina, il cisplatino e la vincristina. Dosi di radioterapia.
Caratteristiche delle seconde neoplasie: tra i sette bambini con seconde neoplasie, cinque bambini avevano la leucemia (quattro leucemia mieloide acuta e un bambino la leucemia linfoblastica B acuta), un bambino aveva la sindrome mielodisplastica e un bambino aveva sarcoma mieloide. Inoltre, tra questi sette bambini, quattro (4/7) avevano cromosomi anomali, due bambini erano normali e un bambino ha rinunciato al trattamento e ha subito il test cromosomico dopo la diagnosi di seconde neoplasie.
Conclusione: L'incidenza dell'insorgenza secondaria di seconde neoplasie nei bambini con tumori solidi maligni non è elevata, considerando che ciò è correlato all'uso di agenti alchilanti, inibitori della topoisomerasi II, farmaci chemioterapici a base di platino e radioterapia e associati alle anomalie cromosomiche.

References

1. Demoor-Goldschmidt C, de Vathaire F: *Review of risk factors of secondary cancers among cancer survivors*. Br J Radiol, 2018; 20180390. doi: 10.1259/bjr.20180390.

2. Perera FP: *Environment and cancer: Who are susceptible?* Science, 1997; 278:1068-73.

3. Meadows AT, D'Angio GJ, Evans AE, Harris CC, Miller RW, Mike V: *Oncogenesis and other late effects of cancer treatment in children.* Radiology, 1975; ,114:175-80.

4. Meadows AT, D'Angio GJ, Miké V, Banfi A, Harris C, Jenkin RD, Schwartz A: *Patterns of second malignant neoplasms in children.* Cancer, 1977; 40:1903-911.doi: 10.1002/1097-0142.

5. Tucker MA, Meadows AT, Boice JD Jr, Stovall M, Oberlin O, Stone BJ, Birch J, Voûte PA, Hoover RN, Fraumeni JF Jr: *Leukemia after therapy with alkylating agents for childhood cancer*. J Natl Cancer Inst, 1987; 78:459-64.

6. Olsen JH, Garwicz S, Hertz H, Jonmundsson G, Langmark F, Lanning M, Lie SO, Moe PJ, Møller T, Sankila R, et al.:. *Second malignant neoplasms after cancer in childhood or adolescence. Nordic society of paediatric haematology and oncology association of the nordic*

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cancer registries. BMJ, 1993; 307:1030-36.doi: 10.1136/bmj.307.6911.1030

7. Breslow NE, Lange JM, Friedman DL, Green DM, Hawkins MM, Murphy MF, Neglia JP, Olsen JH, Peterson SM, Stiller CA, Robison LL: *Secondary malignant neoplasms after Wilms tumor: An international collaborative study*. Int J Cancer, 2010; 127:657-66. doi: 10.1002/ijc.25067.

8. Shimatani A, Aono M, Hoshi M, Oebisu N, Iwai T, Takada N, Hara J, Nitani C, Nakamura H: *Secondary osteosarcoma in patients previously treated for childhood cancer: Three case reports*. Mol Clin Oncol, 2019; 10:153-158. doi: 10.3892/mco.2018.1752.

9. Le Deley MC, Leblanc T, Shamsaldin A, Raquin MA, Lacour B, Sommelet D, Chompret A, Cayuela JM, Bayle C, Bernheim A, de Vathaire F, Vassal G, Hill C; Société Française d'Oncologie Pédiatrique: *Risk of secondary leukemia after a solid tumor in childhood according to the dose of epipodophyllotoxins and anthracyclines: A case-control study by the Société Française d'Oncologie Pédiatrique*. J Clin Oncol, 2003; 21:1074-81.

10. Henderson TO, Rajaraman P, Stovall M, Constine LS, Olive A, Smith SA, Mertens A, Meadows A, Neglia JP, Hammond S, Whitton J, Inskip PD, Robison LL, Diller L: *Risk factors associated with secondary sarcomas in childhood cancer survivors: a report from the childhood cancer survivor study*. Int J Radiat Oncol Biol, Phys, 2012; 84:224-30. doi: 10.1016/j.ijrobp.2011.11.022.

11. Henderson TO, Moskowitz CS, Chou JF, Bradbury AR, Neglia JP, Dang CT, Onel K, Novetsky Friedman D, Bhatia S, Strong LC, Stovall M, Kenney LB, Barnea D, Lorenzi E, Hammond S, Leisenring WM, Robison LL, Armstrong GT, Diller LR, Oeffinger KC: *Breast cancer risk in childhood cancer survivors without a history of chest radiotherapy: A report from the childhood cancer survivor study*. J Clin Oncol,2016 20;34:910-8. doi: 10.1200/JCO.2015.62.3314.

12. Schwartz B, Benadjaoud MA, Cléro E, Haddy N, El-Fayech C, Guibout C, Teinturier C, Oberlin O, Veres C, Pacquement H, Munzer M, N'guyen TD, Bondiau 2014; 53:381-90. doi: 10.1007/s00411-013-0510-9.

13. Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P: *International classification of childhood cancer*. III edition, Cancer, 2005; 103:1457-67.

14. Tukenova M, Diallo I, Hawkins M, Guibout C, Quiniou E, Pacquement H, Dhermain F, Shamsaldin A, Oberlin O, de Vathaire F: *Long-term mortality from second malignant neoplasms in 5-year survivors of solid childhood tumors: Temporal pattern of risk according to type of treatment*. Cancer Epidemiol Biomarkers Prev, 2010; 19:707-15. doi: 10.1158/1055-9965.

15. Varan A, Kebudi R: *Secondary malignant neoplasms after childhood cancer*. Pediatr Hematol Oncol, 2011; 28:345-53. doi: 10.3109/08880018.2011.553879.

16. Teepen JC, van Leeuwen FE, Tissing WJ, van Dulmen-den Broeder E, van den Heuvel-Eibrink MM, van der Pal HJ, Loonen JJ, Bresters D, Versluys B, Neggers SJCMM, Jaspers MWM, Hauptmann M, van der Heiden-van der Loo M, Visser O, Kremer LCM, Ronckers CM: *DCOG LATER Study. Long-term risk of subsequent malignant neoplasms after treatment of childhood cancer in the dcog later study cohort: Role of chemotherapy*. J Clin Oncol, 2017; 35:2288-2298. doi: 10.1200/JCO.2016.71.6902.

17. Zong X, Pole JD, Grundy PE, Mahmud SM, Parker L, Hung RJ: *Second malignant neoplasms after childhood non-central nervous system embryonal tumours in North America: A population-based study*. Eur J Cancer, 2017; 84:173-83. doi: 10.1016/j.ejca.2017.06.035.

18. Ezoe S: *Secondary leukemia associated with the anti-cancer agent, etoposide, atopoisomerase II inhibito*r. Int J Environ Res Public Health/ 2012; 9: 2444–453. doi: https:// doi. org/ 10. 3390/ijerph9072444

19. Travis LB, Holowaty EJ, Bergfeldt K, Lynch CF, Kohler BA, Wiklund T, Curtis RE, Hall P, Andersson M, Pukkala E, Sturgeon J, Stovall M: *Risk of leukemia after platinum-based chemotherapy for ovarian cancer*. N Engl J Med, 19994;340:351-7. doi: 10.1056/NEJM199902043400504

20. Choi DK, Helenowski I, Hijiya N: *Secondary malignancies in pediatric cancer survivors: Perspectives and review of the literatur*e. Int J Cancer, 2014; 15;135:1764-773. doi: 10.1002/ijc.28991.

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