Long-Term Follow-Up of Children Treated for Acute Leukemia Focusing on Development of Malignant and Non-Malignant Neoplasms

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Abstract

Although the introduction of modern treatment strategies has resulted in an excellent prognosis for leukemia, it is also associated with various late effects. Survival data from all children with leukemia diagnosed after 1946 were used to calculate survival rates. Analyses of late effects were performed on patients diagnosed after 1968. The survival rate before 1964 was 0.0 at 302 months (n=240) for acute leukemia and 0.937 ± 0.031 at 212 months (n=64) for Acute Lymphocytic Leukemia (ALL) after 1966. Second Primary Neoplasms (SPNs) developed in 11 survivors with ALL, but in none with AML: 2 breast carcinomas, 1 colon carcinoma, 1 urinary bladder carcinoma, 2 thyroid carcinomas, 1 thyroid adenoma, and 4 meningiomas. The overall incidence of SPNs 29 years after the diagnosis of primary cancers was 10.0%. Furthermore, intracranial cavernous hemangiomas were detected in 3 patients 13 to 31 years after cranial irradiation. In addition to the well-known finding that patients treated with Prophylactic Cranial Irradiation (PCI) are at risk of developing brain tumors, this study revealed that thyroid carcinoma may develop even after PCI if patients are very young. Furthermore, cavernous hemangioma may be one of the serious complications of cranial irradiation because it may result in intracranial hemorrhage. Its symptomatic form appears to be rare but can be potentially serious condition because it is frequently detected by MRI screening. Although the prognosis of leukemia in Japan has markedly improved, this improvement has been associated with serious health issues. Lifelong follow-ups are needed for the survivors of childhood leukemia.

Keywords: Acute lymphoblastic leukemia; Second primary neoplasms; Cavernous hemangioma; Meningioma

Introduction

Although many prognostic factors have been proposed [1], the most influential prognostic factor for childhood leukemia is the treatment used [2,3]. However, the introduction of modern treatment strategies has inevitably resulted in various late effects in long-term survivors. Many review papers concerning the late effects as well as study papers from individual institutes or study group [4-9], such as Children’s Cancer Study Group [10] and Tokyo Children’s Cancer Study Group have been published. However, to design to quantify and better understand the pediatric cancer, it was felt that well organized patient recruitment system is required and for this purpose the Children’s Cancer Survivor Study was formed [11,12]. As the result, the papers about late effects in long-term survivors tended to include a huge number of cases [13,14]. However, these long-term survivor studies were specialized to analyze late effects, although it is important to know possible late effects to give appropriate care to survivors, each caregiver who must explain treatment, it’s possible outcome and possible late effects as well as immediate side effects, should know how prognosis of diseases of their patients has improved and what is the relationship between such treatment and late effects. Here, we examined these late effects in patients who were diagnosed 38 years ago after the introduction of modern treatment strategies in our hospital and affiliated hospitals.

Materials and Methods

The survival data of all children diagnosed with childhood leukemia after 1946 and whose medical records were available were used to calculate survival curves by the Kaplan-Meyer method.
Detailed analyses of late effects were performed using information from patients diagnosed after 1964.

Classification

The classification of acute leukemia markedly changed in 1977 when one of the authors introduced a classification method that was widely used in the United States of America (new system) and a treatment strategy according to Study VIII at St. Jude Children’s Research Hospital, Memphis, Tennessee, U.S.A. Prior to 1977, our hospital and affiliated hospitals used a unique classification system (the old system) [15]. Cases of acute leukemia diagnosed between 1964 and 1976 were reclassified according to the new system. Differences in and the findings of comparisons of both classification systems, namely, the old and new systems, were previously reported [15]. To calculate survival curves, all types of acute leukemia before 1964 were simply classified as acute leukemia, while Acute Lymphocytic Leukemia (ALL) and Acute Myelogenous Leukemia (AML) were differentiated after 1977.

Treatment

Prior to 1963 (Period 1), treatments were mainly supportive, and many children were sent home just after their diagnosis or received blood transfusions only. At the end of this period, some children received large doses of steroid hormones (mPred) [16]. Between 1964 and 1976 (Period 2), mPred therapy was administered to most children with acute leukoblastic leukemia (a subtype of ALL [15]), and during the end of this period, Vincristine (VCR) was added to induction therapy for some children and 6-Mercapturine (6-MP), Methotrexate (MTX), cyclophosphamide, or cytosine arabinoside was administered for maintenance therapy. Central Nervous System (CNS) prophylaxis, including cranial irradiation and an Intrathecal MTX injection (IT-MTX), was also performed for some children; however, the irradiation field was inappropriate. Between 1977 and 1985 (Period 3), we used our own treatment protocol or the Tokyo Children’s Cancer Study Group (TCCSG) protocols. Our own treatment protocol included VCR, daunomycin, and mPred for induction, IT-MTX and CNS irradiation for CNS leukemia prophylaxis, and weekly MTX and daily 6-MP for maintenance therapy. After 1986 (Periods 4 and 5), we used the TCCSG treatment protocols [17], which incorporated the Berlin-Frankfurt-Munch group (BFM)-like protocol. Cranial irradiation was performed on 42 males and 18 females out of the 89 20-year ALL survivors received, but on none of the AML survivors. AML was treated with the TCCSG protocols [18,19].

Follow-up

We followed up these patients by asking them to visit outpatient clinics, sending them greeting cards, occasional phone calls, or sending questionnaires for detailed information. The use of questionnaires was approved by the Institutional Ethical Committee of Kyorin University.

Statistical analysis

Statistical analyses were conducted with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [20] and Kalan-Meyer analyses for survival were performed with SPSS 13.0 for Windows (Mapinfo Corporation, Troy, NY, USA). The level of significance was set at P<0.05.

Results

Follow-up rates

Forty-five (11.1%) out of 405 patients were lost to the follow-up. The parents of 2 patients refused our contact due to concerns that their children may learn of their diagnoses through our communications. It was not possible to locate several other patients after they had been referred to internists; their doctors stopped their follow-up due to their healthy conditions.

Survival rates

Six hundred and forty-five patients were diagnosed with acute leukemia at our hospital and affiliated institutes, and 158 patients were alive as of January 01st, 2014 (Table 1). Survival curves were shown in Figure 1. The survival rate of acute leukemia in Period 1 was 0.0 at 302 months (n=240), while those for ALL were 0.095 ± 0.024 at 583 months in Period 2 (n=158), 0.501 ± 0.060 at 439 months in Period 3 (n=71), 0.753 ± 0.065 at 334 months in Period 4 (n=61), and 0.937 ± 0.031 at 212 months in Period 5 (n=64). The survival rate for AML was 0.538 ± 0.076 (n=51).

Eighty-nine out of 297 patients with ALL and 15 out of 63 patients with AML who kept in contact were alive after more than 20 years.
The mean ages at diagnosis of 89 ALL 20-year survivors were 5 years 8 months (range: 1 year 2 months to 15 years 0 month) for males and 5 years 1 month (1 year 0 month to 12 years 11 months) for females, while those of 15 AML 20-year survivors were 5 years 10 months (1 year 9 months to 14 year 1 month) for males and 6 years 1 month (0 year 9 months to 11 years 3 months) for females.

The mean ages at the study of ALL 20-year survivors were 37 years 5 months (25 years 1 month to 53 years 11 months) for males and 34 years 3 months (23 years 1 month to 53 years 7 months) for females, while those of AML 20-year survivors were 35 years 9 months (22 years 4 months to 46 years 6 months) for males and 36 years 5 months (23 years 2 months to 49 years 3 months) for females.

### Major late effects in patients with ALL

SPNs developed in 11 20-year survivors with ALL (Table 2 and 3), but in none with AML. These SPNs were 2 breast carcinomas, 1 colon carcinoma, 1 urinary bladder carcinoma, 2 thyroid carcinomas, 1 thyroid adenoma, and 4 meningiomas. All meningiomas occurred in 60 patients (42 males and 18 females) treated with CNS irradiation 15 to 28 years after CNS irradiation and all meningioma patients were female (Table 3). The initial symptoms and signs of meningiomas were seizure in 2 patients, headache in 1 and hearing loss in 1.

The overall incidence of SPNs 29 years after the diagnosis of primary cancers was 10.0%. When patients with meningioma and thyroid adenoma and patients with AML were excluded, the overall incidence of Second Primary Malignancies (SPM) 29 years after the diagnosis of ALL was 4.2%.

In 3 patients, intracranial cavernous hemangioma occurred 13 years, 30 years, and 31 years after CNS irradiation. Events

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**Table 2: Development of second primary neoplasms (except for meningioma).**

<table>
<thead>
<tr>
<th>Patients</th>
<th>Sex</th>
<th>Age at diagnoses</th>
<th>Original diseases</th>
<th>2nd neoplasms</th>
<th>Age at second neoplasms</th>
<th>Supposed causes</th>
<th>Outcome</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>EA</td>
<td>F</td>
<td>1y 2m</td>
<td>ALL with CNS</td>
<td>Carcinoma, thyroid</td>
<td>22y 7m</td>
<td>Irradiation to CNS</td>
<td>Resected</td>
<td>Estimated thyroid dose: 1.2Gy</td>
</tr>
<tr>
<td>YTa</td>
<td>M</td>
<td>4y 1m</td>
<td>ALL BM &amp; testis relapses</td>
<td>Carcinoma, thyroid</td>
<td>25y 8m</td>
<td>CSI 18Gy, auto-PBSCT</td>
<td>Expired</td>
<td>CNS prophylaxis + CSI</td>
</tr>
<tr>
<td>YI</td>
<td>M</td>
<td>3y 4m</td>
<td>ALL</td>
<td>Carcinoma, bladder</td>
<td>47y 2m</td>
<td>Unknown</td>
<td>Resected</td>
<td></td>
</tr>
<tr>
<td>RY</td>
<td>F</td>
<td>3y 6m</td>
<td>ALL</td>
<td>Carcinoma, breast</td>
<td>48y 6m</td>
<td>Unknown</td>
<td>Resected</td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>F</td>
<td>12y 11m</td>
<td>ALL</td>
<td>Carcinoma, breast</td>
<td>33y</td>
<td>Unknown</td>
<td>Resected</td>
<td></td>
</tr>
<tr>
<td>YTu</td>
<td>M</td>
<td>5y 4m</td>
<td>ALL BM relapse</td>
<td>Carcinoma, colon</td>
<td>38y</td>
<td>CYC</td>
<td>Resected</td>
<td>CYC 7.5 g/ m² after BM relapse</td>
</tr>
<tr>
<td>TI</td>
<td>M</td>
<td>9y 11m</td>
<td>ALL, Ph1</td>
<td>Adenoma, thyroid</td>
<td>21y 6m</td>
<td>TB12Gy, allo-HSCT</td>
<td>Expired</td>
<td></td>
</tr>
</tbody>
</table>

**Table 3: Intracranial events.**

<table>
<thead>
<tr>
<th>Patients</th>
<th>Sex</th>
<th>Age at diagnosis of original disease</th>
<th>Age at events</th>
<th>Age at irradiation</th>
<th>Time from irradiation to events (years)</th>
<th>Radiation dose (Gy)</th>
<th>Signs &amp; symptoms of meningioma</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>KM</td>
<td>F</td>
<td>2y 4m</td>
<td>28y 6m</td>
<td>2y 5m</td>
<td>26</td>
<td>24</td>
<td>Headache</td>
<td></td>
</tr>
<tr>
<td>AT</td>
<td>F</td>
<td>3y 0m</td>
<td>32y 0m</td>
<td>3y 1m</td>
<td>29</td>
<td>30</td>
<td>Seizure</td>
<td>CNS involvement at diagnosis</td>
</tr>
<tr>
<td>SS</td>
<td>F</td>
<td>3y 1m</td>
<td>22y 10m</td>
<td>3y 2m</td>
<td>19</td>
<td>18</td>
<td>Seizure</td>
<td></td>
</tr>
<tr>
<td>CS</td>
<td>F</td>
<td>3y 9m</td>
<td>19y 3m</td>
<td>3y 10m*</td>
<td>16</td>
<td>18+18**</td>
<td>Hearing loss</td>
<td>12Gy for TBI + 6Gy to CNS after BM relapse</td>
</tr>
</tbody>
</table>

**Table 4: Very late relapses.**

<table>
<thead>
<tr>
<th>Patients</th>
<th>Sex</th>
<th>Ages at diagnosis</th>
<th>Phenotypes</th>
<th>Duration of CCR</th>
<th>Ages at death</th>
<th>Survival time</th>
<th>Relapses</th>
</tr>
</thead>
<tbody>
<tr>
<td>YT</td>
<td>M</td>
<td>7y 11m</td>
<td>Non-B, Non-T</td>
<td>14y 3m</td>
<td>24y 4m</td>
<td>16y 5m</td>
<td>Bone marrow B-precursor</td>
</tr>
<tr>
<td>FN</td>
<td>F</td>
<td>3y 1m</td>
<td>Non-B, Non-T</td>
<td>19y 8m</td>
<td>24y 11m</td>
<td>21y 9m</td>
<td>Bone marrow B-precursor</td>
</tr>
<tr>
<td>TT</td>
<td>M</td>
<td>13y 6m</td>
<td>Non-B, Non-T</td>
<td>33y 7m</td>
<td>49y 3m</td>
<td>35y 9m</td>
<td>Bone marrow B-precursor</td>
</tr>
</tbody>
</table>

(20-year survivors). The mean ages at diagnosis of 89 ALL 20-year survivors were 5 years 8 months (range: 1 year 2 months to 15 years 0 month) for males and 5 years 1 month (1 year 0 month to 12 years 11 months) for females, while those of 15 AML 20-year survivors were 5 years 10 months (1 year 9 months to 14 year 1 month) for males and 6 years 1 month (0 year 9 months to 11 years 3 months) for females. The mean ages at the study of ALL 20-year survivors were 37 years 5 months (25 years 1 month to 53 years 11 months) for males and 34 years 3 months (23 years 1 month to 53 years 7 months) for females, while those of AML 20-year survivors were 35 years 9 months (22 years 4 months to 46 years 6 months) for males and 36 years 5 months (23 years 2 months to 49 years 3 months) for females.

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The overall incidence of SPNs 29 years after the diagnosis of primary cancers was 10.0%. When patients with meningioma and thyroid adenoma and patients with AML were excluded, the overall incidence of Second Primary Malignancies (SPM) 29 years after the diagnosis of ALL was 4.2%.

In 3 patients, intracranial cavernous hemangioma occurred 13 years, 30 years, and 31 years after CNS irradiation (Table 3). Events
for the discovery of hemangioma were pons hemorrhage in 1 female patient, a Magnetic Resonance Imaging (MRI) study for vertigo in 1 male patient, and an MRI study for depression in 1 male patient. It currently remains unclear whether these symptoms in male patients were related to hemangiomas because they improved without any physical intervention. The female patient had another hemorrhage in the right parietal lobe which left some mild sequelae, such as forgetfulness, mild left facial nerve palsy, and petit mal seizure.

Three ALL patients relapsed in bone marrow without extramedullary disease 14, 19 and 33 years after Continuous Complete Remission (CCR) and all died in second remission despite stem cell transplantation (Table 4). A detailed case report of a male patient who relapsed 34 years after the initial diagnosis has already been published [21]. In the remaining 2 patients, since lymphoblasts had the B-precursor phenotype and a similar morphological feature to those at the initial diagnosis, which was also the non-B non-T phenotype, we considered these patients to have relapsed ALL rather than secondary ALL; however, detailed lineage analyses were not available.

Discussion

A large gap exists in survival data between Periods 2 and 3. Although leukemia in Period 2 included cases of ALL and AML, the number of cases of AML was inadequate to reduce the survival rate of leukemia; therefore, we consider this gap to have appeared due to actual improvements in the treatment of ALL.

It is important to note that 3 deaths among patients with ALL occurred 16, 21 and 35 years after CCR for 14, 19 and 33 years, respectively. We considered the reappearance of ALL blasts in these patients to have indicated relapse rather than second malignancies because the immunophenotype was the same; however, we confirmed in only one patient that the leukemic clones that reappeared were the same as those in the initial diagnosis. Although relapse after CCR for 10 years is very rare in the modern treatment era [7], it does occur.

Six patients developed SPM. The estimated risk of SPNs 29 years after the diagnosis of leukemia was 10.0%. This result is consistent with previous reports [8,14], and when patients with non-malignant neoplasms and those with AML were excluded from SPNs, the risk of SPM was similar to a previous study in Japan in which the estimated risk was 2.4% at 20 years [11]. The age of patients at the diagnosis of these malignancies was younger than that of the general population. Less than 4% of cases of the given cancers were related to hemangiomas because they improved without any physical intervention. The female patient had another hemorrhage in the right parietal lobe which left some mild sequelae, such as forgetfulness, mild left facial nerve palsy, and petit mal seizure.

Patients treated with PCI of CNS leukemia are at risk of developing brain tumors [10]. Although meningioma is most frequent type of radiation-induced brain tumor, the distribution of various kinds of radiation-induced brain tumors depends on age at irradiation, the radiation dose, and length of the follow-up. A lower radiation dose, older age at irradiation, and longer follow-up are associated with the development of meningioma [13,23,24]. Brain tumors in our patients were meningiomas only. The reason for this imbalance currently remains unclear but may be attributed to the small number of patients examined in the present study. Meningioma typically develops in elderly patients; however, the ages of our patients that developed meningioma were younger than that of the general population, with only 5% of meningioma cases developing meningioma before 35 years of age [25]. All meningioma cases received PCI and were female. Although meningioma develops more frequently in females than in males, particularly as age increases, this female preponderance was not clearly observed for radiation-induced meningioma [26]. One of reasons may be that radiation-induced meningiomas tend to occur in patients of relatively younger ages as seen in our patients.

One out of the 2 thyroid carcinomas occurred in a female patient who received CNS radiotherapy of 24 Gy at 1 year of age for CNS leukemia. The estimated thyroid dose of CNS irradiation was approximately 7% of the CNS dose [27], namely, approximately 1.7 Gy for this patient. This radiation dose may have caused thyroid carcinoma [28]. Another male patient who relapsed in his bone marrow and tests and had peripheral blood stem cell auto-transplantation with 18 Gy of craniospinal irradiation and 20 Gy of irradiation to the test is developed thyroid medullary carcinoma. This patient also received 18 Gy of PCI at the time of the initial treatment. The Life Span Study in Hiroshima showed a higher incidence of thyroid cancer in younger age groups [29], even at very low radiation doses with an average of 0.7 Gy, particularly in females. Socié et al. [30] reported 4 cases of thyroid cancer among 3,182 cases that underwent Hematopoietic Stem Cell Transplantation (HSCT) at a median age of 8.1 years (range: 5.5-9.2). These patients received Total Body Irradiation (TBI) in addition to cranial irradiation. Ho et al. [31] reported 6 cases of thyroid cancer in ALL. Only one female patient received cranial irradiation only and the remaining 5 patients had HSCT and TBI. Pui et al. [7] included 4 cases of thyroid carcinoma among 597 irradiated patients in their findings from an extended follow-up of long-term survivors of ALL; however, information on the types of radiation used was not provided. A report from the Childhood Cancer Survivor Study [13] included 16 cases of thyroid carcinoma among 2,457 irradiated survivors, some of whom had HSCT and TBI. Thus, thyroid cancer as the second malignant disease in ALL patients appears to be rare without HSCT.

It is important to note that intracranial cavernous hemangioma developed in 3 patients with PCI 13 to 31 years after irradiation. Humpl et al. [32] reported that 4 out of 120 ALL patients with PCI developed cavernous hemangiomas 2 to 12 years after this treatment; therefore, cavernous hemangioma may develop even in patients treated with PCI at relatively lower dosages after various latencies. Strenger et al. [33] found that 1 patient had cavernous hemangioma in 8 out of 171 patients treated with cranial irradiation, including 3 out of 83 leukemia patients; all these patients were asymptomatic, and their cavernous hemangioma were detected in routine follow-up studies 8.5 to 18.4 years after PCI for leukemia. Although Pui et al. [7] reported the findings of an extended follow-up of 856 long-term survivors of childhood ALL, their table of adverse events did not include cavernous hemangioma despite the inclusion of intracranial events, such as meningioma and malignant brain tumors. Thus, the occurrence of cavernous hemangioma appears to be a rare event after cranial irradiation for leukemia, particularly in the case of prophylaxis. However, Faraci et al. [34] reported that although only 2 patients developed symptomatic cavernous hemangiomas, MRI screening after PCI or TBI for stem cell transplantation for leukemia revealed cavernous hemangiomas in 57% of patients. According to their report, the incidence of cavernous hemangioma after cranial irradiation appeared to be extremely high and symptomatic patients may merely be the tip of the iceberg. Although the latency of the development of cavernous hemangioma...
following cranial irradiation may be short in some patients, very long latency is not rare. Cavernous hemangioma and meningioma are well-known sequelae of cranial irradiation and the concurrent development of both lesions has been reported [35]. Although most cases of meningioma were symptomatic, large numbers of cavernous hemangioma cases were asymptomatic and incidentally detected during examinations for other conditions or routine screening. However, some patients developed symptoms and signs. The most frequent symptom and sign was seizure, and even hemorrhage was detected, as in our patient. According to Nimjee et al. [36], 37 out of 76 reported patients, including 12 ALL patients, exhibited evidence of hemorrhage, with many requiring surgical interventions. The reason for the earlier diagnosis of cavernous hemangioma in one of our patients may be that this patient's disease was symptomatic. Asymptomatic disease is more likely to be diagnosed incidentally and a longer time after irradiation. These findings indicate the necessity for periodical screening with MRI among patients treated with irradiation to various fields including the brain.

Two patients developed breast carcinomas and 1 colon carcinoma in non-irradiated parts of the bodies, although they received possible carcinogenic drugs after relapse, except for 1 female patient with breast cancer. The relationship between meningioma and breast carcinoma has repeatedly been reported [37-41], with only one negative report to date [42], and that between meningioma and colorectal carcinoma has also been demonstrated [43]. Association of these cancers with meningioma may be incidental because both types of cancers are those of most common types of cancers in general population [11]; however, this association, if confirmed, will be useful to define targets for follow-up of survivors.

The CCG study showed that the incidence of SPN decreased among ALL cases diagnosed after 1983 [44]. One of the major reasons for this lowered incidence appears to be related to the lowered usage of cranial irradiation, because the TCCSG study showed that the incidence of second cancers in ALL correlated with cranial irradiation as well as the duration of the follow-up [11]. We expect the incidence of SPNs in our patient cohort after Period 4 to markedly decrease because cranial irradiation was omitted in most patients in this cohort.

Large numbers of patients have been lost to the follow-up. One of the main reasons for this is that most patients had not been informed of their diagnosis. Until recently, it was customary in Japan for pediatric patients with cancers to not be informed of their diagnoses; therefore, some parents whose children have become adults have not told them of the diagnoses of their diseases and, thus, our direct contact with their children in adulthood is not possible. Therefore, it is impossible to collect detailed information on the pathological findings of second neoplasms in some patients, which is the limitation of our study.

Conclusion

The prognosis of leukemia in Japan has markedly improved since the introduction of modern treatment strategies. However, this improvement has been associated with various late effects in long-term survivors. Among these health issues, the development of second neoplasms and related intracranial lesions is the most serious. Long, possibly lifelong follow-ups are needed for the survivors of childhood leukemia. It is important to share all information with the patients themselves in addition to their parents.

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References

administration of steroid hormone in the therapy of acute infantile leukemia—with special reference to the authors' cases. Saishin Igaku 1966;21:557–67. (In Japanese)


22. Monitoring of Cancer Incidence in Japan 2012 (MCJ2012). Center for Cancer Control and Information Center, National Cancer Center.


