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Treatment of Isolated Testicular Recurrence of Acute Lymphoblastic Leukemia without Radiotherapy
Report from the Dutch Late Effects Study Group

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BACKGROUND. The isolated recurrence of testicular leukemia in boys with acute lymphoblastic leukemia (ALL) is considered to be an ominous sign, heralding generalized recurrence. In general, treatment is comprised of systemic retreatment and local radiotherapy to one or both affected testes.

METHODS. In this study, the authors report five boys with a late isolated testicular recurrence of ALL during sustained bone marrow remission, in whom radiotherapy had been omitted. High-dose methotrexate was included in the treatment regimen.

RESULTS. No further recurrences occurred after cessation of therapy. The follow-up period ranged from 1–15 years (median, 8 years).

CONCLUSIONS. These cases show that there is a subpopulation of boys with recurrence of testicular leukemia who can be treated without radiotherapy. Therefore, the authors propose a treatment regimen for boys with late isolated recurrence of testicular leukemia in which conventional reinduction maintenance treatment is given in combination with high-dose methotrexate. Radiotherapy should be withheld until subsequent testicular recurrence occurs. Cancer 1997;79:2257–62.
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KEYWORDS: acute lymphoblastic leukemia, recurrence, testicle, children, methotrexate, radiotherapy, residual disease.

Testicular leukemia may be an obstacle in the treatment of boys with acute lymphoblastic leukemia (ALL). Before 1960, testicular involvement was rarely observed. With the significant improvement of survival in the past decades, an increase in the testicular recurrence rate occurred; the reported frequency of overt testicular recurrence in children with ALL ranges between 0.9–8.8%.¹² These recurrences occur mainly during bone marrow disease remission. Because testicular recurrence, like other types of extramedullary recurrence, should be considered to be a harbinger of bone marrow recurrence, these patients receive a full retreatment regimen. In all reports studied, radiotherapy has been given to one or both testicles. In this article, the authors describe five cases in which radiotherapy could be avoided, probably by including (very) high-dose methotrexate in the treatment regimen.

MATERIALS AND METHODS
Patients
All patients who had ALL treated at the study hospital from 1975 onward were considered in the analysis. Only those who achieved complete remission and who developed testicular infiltration without involvement of bone marrow and/or other sites were considered. Six
TABLE 1
Characteristics at Initial Diagnosis

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Peripheral blood</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukocytes (10^9/l)</td>
<td>5.8</td>
<td>171</td>
<td>10.3</td>
<td>3.9</td>
<td>4.2</td>
</tr>
<tr>
<td>Blasts (%)</td>
<td>7</td>
<td>80</td>
<td>39</td>
<td>0</td>
<td>37</td>
</tr>
<tr>
<td>Platelets (10^9/l)</td>
<td>90</td>
<td>27</td>
<td>120</td>
<td>16</td>
<td>147</td>
</tr>
<tr>
<td>Bone marrow aspirate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphology</td>
<td>L1</td>
<td>L1</td>
<td>L1</td>
<td>L1</td>
<td>L1</td>
</tr>
<tr>
<td>Immunophenotype</td>
<td>NA</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Karyotype</td>
<td>NA</td>
<td>45X, marker 8, t(15;20)(q15;q11), −16</td>
<td>47,XY,del(6)(q13q21)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Extramedullary involvement</td>
<td>None</td>
<td>Kidney</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

NA: not available.

TABLE 2
Summary of Treatment and Outcome

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interval between end of chemotherapy and recurrence (mos)</td>
<td>8</td>
<td>19</td>
<td>71</td>
<td>24</td>
<td>22</td>
</tr>
<tr>
<td>during maintenance</td>
<td>6x HD-MTX</td>
<td>HD-MTX</td>
<td>Ara-C, teniposide</td>
<td>Ara-C, teniposide</td>
<td>Ara-C, teniposide</td>
</tr>
<tr>
<td>Systemic treatment induction maintenance</td>
<td>Pred, VCR, Asp</td>
<td>Pred, VCR, Asp, MTX, 6-MP</td>
<td>Pred, VCR, Asp</td>
<td>Pred, VCR, Asp, MTX, 6-MP</td>
<td>Pred, VCR, Asp</td>
</tr>
<tr>
<td>Treatment duration (mos)</td>
<td>24</td>
<td>12</td>
<td>12</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Follow-up period from time of recurrence onward (yrs)</td>
<td>15</td>
<td>4</td>
<td>8</td>
<td>1.5</td>
<td>1</td>
</tr>
</tbody>
</table>

VHD: very high dose; MTX: methotrexate; HD: high dose; Pred: prednisone; VCR: vincristine; Asp: L-asparaginase; 6-MP: 6-mercaptopurine; Ara-C: cytosine arabinoside.

RESULTS

Characteristics at diagnosis of all patients are presented in Table 1. A summary of treatment of the recurrence is given in Table 2.

Case 1
Initial therapy was comprised of induction treatment with vincristine and prednisone. Prophylaxis for central nervous system (CNS) recurrence was given using 25-gray cranial irradiation. Maintenance courses of 2 weeks of vincristine (1.5 mg/m^2/week intravenously [i.v.]) and prednisone (40 mg/m^2/day orally) alternated with 5-week courses of 6-mercaptopurine (50 mg/m^2/day orally) and methotrexate (30 mg/m^2/week orally). Therapy was stopped 17 months after initial presentation. In 1980 (8 months after stopping maintenance therapy) swelling of the left testicle was noted; histology revealed infiltration with lymphoblasts. Bone marrow and cerebrospinal fluid were normal. Systemic reinduction was comprised of prednisolone (40 mg/m^2/day orally) for 4 weeks, vincristine (2 mg/m^2/week i.v.) for 4 weeks, and Escherichia coli asparaginase (200 IU/kg/day i.v.) from Days 28–42. On the first
day of reinduction, 2 6-hour infusions with methotrexate (6000 mg/m²) were given. This maintenance treatment was similar to the maintenance treatment used after the initial treatment; however, 6 additional infusions of methotrexate (6000 mg/m²) were added at monthly intervals. Treatment was stopped in 1982, 24 months after reinduction therapy was started. Pubertal development has been normal. At last follow-up, the volumes of both testicles were alike and of normal adult size. The patient’s plasma testosterone level was normal (18.1 µM/L) and luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were not elevated (5.0 U/L and 4.0 U/L; reference values < 15 U/L for both LH and FSH). His sperm count was $31 \times 10^6$ / mL.

**Case 2**
The patient’s initial therapy was comprised of 4 weeks’ induction with vincristine and prednisone. On Days 1 and 21, 6000 mg/m² of methotrexate was given. No CNS irradiation was given. In Week 8, 10, 15, and 18 courses of 6000 mg/m² methotrexate were given. Maintenance treatment was comprised of alternating courses of vincristine, prednisone, 6-mercaptopurine, and methotrexate, as outlined in the report for Case 1. Therapy was stopped 24 months after initial presentation. In 1991 (19 months after stopping maintenance therapy) swelling of both testicles was noted; histology revealed infiltration with lymphoblasts. Immunologic markers were similar to those observed in the lymphoblasts at initial diagnosis. Bone marrow and cerebrospinal fluid were normal. At the start of treatment, 1 6-hour infusion with methotrexate (12,000 mg/m²) was given. Cytosine arabinoside (Ara-C) (1000 mg/m² 1-hour infusion) and teniposide (165 mg/m² 2-hour infusion) were given in Weeks 3 and 11. Systemic reinduction was started 4 weeks after start of treatment for the testicular localization and was comprised of prednisolone (40 mg/m²/day orally) for 4 weeks, vincristine (2 mg/m²/week i.v.) for 4 weeks, and *E. coli* asparaginase (200 IU/kg/day i.v.) during Weeks 8 and 9. Maintenance treatment with 6-mercaptopurine, methotrexate, vincristine, and prednisolone (dosages and intervals as reported in Case 1) was given together with 6 additional infusions of methotrexate (6000 mg/m²), each given at 7-week intervals. Treatment was stopped in 1992, 12 months after reinduction therapy was begun.

At last follow-up, the boy was age 11 years. His right and left testicular volumes were alike and the testicles of prepubertal size.

**Case 3**
The patient’s initial treatment was given according to Protocol V of the Dutch Childhood Leukemia Study Group (DCLSG). Essentially, a standard induction treatment was used, and CNS prophylaxis was given using radiotherapy; no methotrexate was given. In 1987, 71 months after stopping antileukemic treatment, the patient developed right testicular enlargement, which was proven to be a recurrence of the original disease. No other sites were involved. Treatment was essentially the same as reported in Case 2. Treatment for the local recurrence started with high dose methotrexate (12,000 mg/m² in a single 6-hour infusion) and was combined with teniposide (165 mg/m² 2-hour infusion) and Ara-C (1000 mg/m² 1-hour infusion), given on the same day. Systemic reinduction was started after 1 week and was comprised of prednisolone (40 mg/m²/day orally) for 4 weeks, vincristine (2 mg/m²/week i.v.) for 4 weeks, and *E. coli* asparaginase (200 IU/kg/day i.v.) from Days 28–42. After 8 weeks, Ara-C (1000 mg/m² 1-hour infusion) and teniposide (165 mg/m² 2-hour infusion) were given. During maintenance treatment, courses of 2 weeks of vincristine (1.5 mg/m² week i.v.), teniposide (165 mg/m² i.v. given once), Ara-C (1000 mg/m²/week i.v.), and prednisone (40 mg/m²/day) alternating with 4-week courses with 6-mercaptopurine (50 mg/m²/day orally) and methotrexate (30 mg/m²/week orally) were given. Treatment was stopped in 1988, 12 months after diagnosis of recurrence. Pubertal development has been normal. At last follow-up, the patient’s plasma testosterone level was normal (24 µM/L), and LH and FSH were not elevated (4.0 U/L and 7.0 U/L). Volumes of both testicles were alike and they were of normal adult size. A sperm count of $2.3 \times 10^6$ mL was noted.

**Case 4**
Initial treatment was given according to Protocol VI of DCLSG. Essentially, a standard induction treatment and CNS prophylaxis using methotrexate was given. Therapy was stopped 26 months after initial diagnosis. In 1994, 70 months after initial diagnosis, the patient developed right testicular enlargement, which was proven to be a recurrence of the original disease. Treatment was comprised of high dose methotrexate (12,000 mg/m² in a 6-hour infusion); teniposide (165 mg/m² i.v.) and Ara-C (1000 mg/m² i.v.) were given 3 weeks after the initiation of treatment. Systemic reinduction started 1 week later and was comprised of prednisolone (40 mg/m²/day orally for 4 weeks), vincristine (2 mg/m²/week i.v. for 4 weeks), and *E. coli* asparaginase (200 IU/kg/day i.v. from Days 28–42). In addition, 11 weeks after initiation of treatment, teniposide (165 mg/m² i.v.) and Ara-C (1000 mg/m² i.v.) were given. Maintenance therapy was comprised of 49-day courses of methotrexate (5000 mg/m² on Day 1 of each course), teniposide (165 mg/m² on Day 7) and Ara-C.
(1000 mg/m² i.v. on Day 7), vincristine (1.5 mg/m² i.v. on Days 1 and 7), 6-mercaptopurine (50 mg/m²/day orally from Days 14–49), and methotrexate (30 mg/m²/week orally from Days 14–49). Treatment was stopped 13 months after the start of reinduction. At last follow-up, the testicular volumes of this 9-year-old boy were alike and his testicles were of normal prepubertal size.

Case 5
Treatment was given according to the standard risk regimen of the ALL-BFM 86 protocol.⁵ Treatment was given for 18 months. In 1994, 22 months after the end of initial treatment, a recurrence in the right testicle was histologically confirmed. Therapy to treat this recurrence was similar to the treatment for recurrence in Case 4. At last follow-up, pubertal development was beginning at the age of 15 years. The patient’s testicular volumes were alike and both testicles showed normal pubertal growth (5 mL at latest examination).

DISCUSSION
Advances in the management of childhood leukemia have introduced new problems and new questions, and the significance of testicular leukemia is currently under debate. Some have regarded the testes, like the CNS, as a sanctuary wherein leukemic cells are relatively protected from chemotherapeutic agents and from which place they may reseed the bone marrow.⁶,⁷ Others consider the testes as merely a barometer of extramedullary disease, foretelling generalized recurrence.⁸ Recent investigations using polymerase chain reactions (PCR) for leukemia specific sequences have shown that malignant cells can already be present in the bone marrow at the moment of extramedullary recurrence, although microscopically the bone marrow is still in remission.⁹ Although quantification by PCR is not yet totally reliable, figures of 0.1–1.0% are mentioned in regard to the extent of bone marrow infiltration.¹⁰¹¹ Clinical observations (i.e., 1) boys with testicular recurrence treated only locally, by means of radiotherapy, develop a bone marrow recurrence within a few months and 2) the finding of patients with apparently isolated testicular leukemia showing spread to abdominal lymph nodes as verified on samples taken at laparotomy) add to the assumption that testicular leukemia must be considered part of the generalized disease.¹²¹³ Consequently, systemic retreatment is needed. Using modern regimens, another recurrence is still the major event after treatment of isolated testicular recurrence. Combining 5 major reports (i.e., BFM Rez 85, AIEOP, POG 8303, POG 8304, CCG-112), 109 of 231 patients experienced a second recurrence; in 82 patients, the bone marrow was the site of recurrence.⁷,¹⁴–¹⁷ However >60% of the patients with overt testicular recurrence in the mentioned reports had an early testicular recurrence. Based on the fact that patients with isolated testicular recurrence occurring >12 months after the end of chemotherapy did not recur, Uderzo et al. concluded that late isolated recurrence is a truly localized disease.¹⁵ Additional studies regarding the detection of minimal residual disease in bone marrow will provide the ultimate answer in respect to this point. The most important risk factor for outcome after isolated testicular recurrence is the duration of first remission. An especially poor prognosis exists if the recurrence occurs while the patient is still undergoing chemotherapy.¹⁸–²⁰ Current treatment protocols for testicular recurrence invariably contain radiotherapy, mainly for both testes.⁷,¹⁴–¹⁷,¹⁹,²¹ The cases in the current study show that there is at least a subpopulation of boys with testicular recurrence who can be treated with high dose methotrexate without radiotherapy, thus salvaging the testes. However, the follow-up period in the patients in Cases 4 and 5, considering the duration of first remission is too short to state that cure has already been ascertained.

With regard to the role of routine biopsy, Wofford et al. showed that a positive biopsy at the end of initial therapy is indicative of a poorer prognosis.¹⁷ However, comparing these patients with the cases in the current study, it is likely that their patients would have developed an earlier recurrence. As such their results cannot be used for patients with late recurrences. In addition, Buchanan et al. showed that seven of nine patients with an isolated testicular recurrence had negative routine biopsies at the end of antileukemic treatment.¹⁶ The role and scheduling of sonography of the testicles to detect recurrences that are not yet palpable is questionable. Because no early testicular recurrences were noted in the patients in the current study, the authors cannot make any conclusions regarding patients with early isolated recurrences. It has been shown that methotrexate easily reaches the testicular interstitium.²² The clinical efficacy of high dose methotrexate to eradicate leukemic foci in the testes is reflected by the fact that the use of intermediate dose methotrexate in first-line treatment protocols has significantly decreased the frequency of testicular recurrence.²³–²⁵ From the literature, one can conclude that the authors’ mode of treatment is probably relatively safe with regard to side effects to the testicle. No killing of the stem cells of spermatogenesis by the cytostatic agents used has been described in animals.²⁶ Only in rats treated with Ara-C in the neonatal period the number of Sertoli’s cells did decrease.³¹ The occurrence of DNA breaks during spermatogenesis as a re-
sult of treatment with teniposide has been reported; however, no data on long term effects have yet been described.\textsuperscript{32} No long term detrimental effects on spermatogenesis and endocrine function in humans have been described for the drugs used in the current study.\textsuperscript{33–36} However, the impact of methotrexate doses as high as 12,000 mg/m\textsuperscript{2} on testicular function is merely an extrapolation. Because only two patients in the current study underwent semen analysis, no definite conclusion could be drawn. Because one of these patients had an acceptable (although still decreased) sperm count, it may be deduced that the very high dosages of methotrexate used did not seriously interfere with later spermatogenesis.

Based on these observations, the authors propose that boys with isolated testicular recurrence undergo treatment with conventional induction and maintenance schemes combined with high dose methotrexate of at least 12,000 mg/m\textsuperscript{2} without radiotherapy to reduce the chance of future infertility. In those patients who have already received dosages of methotrexate up to 2000 mg/m\textsuperscript{2}, the authors believe that the addition of high dose Ara-C and teniposide may be beneficial. Whether this last hypothesis is correct cannot be concluded from the current study cases. However, these patients do illustrate that radiotherapy is not mandatory in the treatment of a first isolated late testicular recurrence in patients with ALL.

REFERENCES


