Arsenic trioxide in comparison with chemotherapy and bone marrow transplantation for the treatment of relapsed acute promyelocytic leukaemia

W. Y. Au¹, A. K. W. Lie¹, C. S. Chim¹, R. Liang¹, S. K. Ma², C. H. Chan³, Y. K. Mak³, Y. T. Chen³, C. C. So⁴, Y. M. Yeung⁵, S. F. Yip⁵, L. G. Wong⁵, J. C. Chan⁶, S. Y. Liu⁶ & Y. L. Kwong¹*

Departments of ¹Medicine and ²Pathology, Queen Mary Hospital, Hong Kong; Departments of ³Medicine and ⁴Pathology, Queen Elizabeth Hospital, Hong Kong; ²Department of Medicine, Tuen Mun Hospital, Hong Kong; ³Department of Medicine, Pamela Youde Nethersole Eastern Hospital, Hong Kong, People’s Republic of China

Background: The best overall treatment strategy for patients with acute promyelocytic leukaemia (APL) in relapse with chemotherapy, bone marrow transplantation (BMT) or arsenic trioxide (As₂O₃) based therapy remains undefined.

Patients and methods: We reviewed the clinical course and treatment outcome of 143 APL cases seen in four major hospitals in Hong Kong over a 10-year period.

Results: Complete remission (CR) was attained in 113 cases (79%) with all-trans retinoic acid (ATRA) and chemotherapy. Relapse occurred at a median of 16 months in 54 cases, with a 3-year disease free survival of 56%. Post-relapse treatment was successful in 41 cases (76%), giving an actuarial 3-year overall survival (OS) of 81% from CR1. Three different protocols were used: chemotherapy alone (n = 19), allogeneic BMT (n = 14) and an As₂O₃-based regimen (n = 21). Chemotherapy was associated with the highest treatment-related mortality (TRM) at 53%, giving a CR2 rate of 47%. TRM was 36% for BMT. The CR2 rate for the As₂O₃-based regimen was 100%, with no TRM. However, 38% of As₂O₃ treated patients had subsequent relapses, which were further salvaged in 75% by combined As₂O₃ plus ATRA. The actuarial OS for the three protocols leveled off by 2 years at 82% for As₂O₃, 43% for BMT and 23% for chemotherapy (P = 0.0004).

Conclusions: Our results suggest that As₂O₃ may be superior to chemotherapy and BMT for the treatment of APL in relapse.

Key words: acute promyelocytic leukaemia, allogeneic bone marrow transplantation, arsenic trioxide, relapse

Introduction

Acute promyelocytic leukaemia (APL) is characterised by t(15; 17)(q22; q21), which results in PML/RARA gene fusion. It is highly sensitive to all-trans retinoic-acid (ATRA), which acts as a differentiation agent [1], and arsenic trioxide (As₂O₃), which induces both differentiation and apoptosis [2]. Although APL blasts are very sensitive to chemotherapy, particularly anthracyclines [3], induction chemotherapy is associated with early death due mainly to haemorrhagic complications [4]. With the use of ATRA combined with chemotherapy, haemorrhagic complications can largely be avoided. However, up to 20% of patients still relapse, despite the use of chemotherapy and ATRA as consolidation and maintenance treatment [5].

In relapsed APL, the best treatment strategy remains contentious. Some patients are still responsive to ATRA and chemotherapy. Allogeneic bone marrow transplantation (BMT) may give lasting remissions, but the patient selection and timing for BMT are unresolved issues. Clinical and laboratory evidence indicates that As₂O₃ is a highly effective treatment for relapsed APL. However, the role of As₂O₃, in comparison with further chemotherapy or allogeneic BMT, has not hitherto been formally evaluated.

In this report, we studied the treatment results of newly diagnosed and relapsed cases of APL over a 10-year period, with a specific focus on evaluating the relative merits of chemotherapy, allogeneic BMT and As₂O₃ in the treatment of relapses.

Materials and methods

Patients

All patients with APL treated between 1991 and 2001 were included in the analysis. They were treated in four tertiary referral centres (Queen Mary Hospital, Queen Elizabeth Hospital, Tuen Mun Hospital, Pamela Youde Nethersole Eastern Hospital) that served over 70% of leukaemia patients in Hong Kong during that time period. The diagnosis of APL was based on marrow
morphology, and was confirmed by cytogenetic and/or molecular investigations [6].

Treatment of newly diagnosed APL

The standard induction protocol was ATRA (45 mg/m²/day ×6 weeks), together with daunorubicin (50 mg/m²/day ×3 days) and cytosine arabinoside (100 mg/m²/day ×7 days). Consolidation therapy consisted of two to four courses of an anthracycline (daunorubicin or mitoxantrone) containing regimen. Maintenance therapy (ATRA 45 mg/m²/day ×15 every 3 months, methotrexate 15 mg/m²/week, 6-mercaptopurine 50 mg/m²/day for 18 months) was used in three centres. Prospective monitoring of minimal residual leukaemia was not performed routinely.

Treatment of relapsed APL

All relapses were diagnosed by marrow biopsy and confirmed cytogenetically or molecularly (Table 1). From 1991 to 1997, chemotherapy and ATRA were used for induction of second complete remission (CR2) (n = 33). Patients reaching CR2 and with a suitable marrow donor (n = 14) proceeded to allogeneic BMT, while the others (n = 19) received consolidation with conventional chemotherapy. After 1997, As₂O₃ (10 mg/day until remission) and idarubicin (72 mg/m² in nine divided doses over 3 months) were used in all relapsed cases (n = 21), as previously reported [7]. Patients who relapsed again after As₂O₃/idarubicin treatment (n = 8) were further treated with As₂O₃ (10 mg/m²/day) and ATRA (45 mg/m²/day) until CR3, followed by further consolidation with As₂O₃ plus ATRA, each given for 14 days every 4–6 weeks for six courses, as reported previously [8].

Allogeneic BMT

From 1991 to 1997, all relapsed patients reaching CR2 and with a human leukocyte antigen (HLA)-identical donor (n = 14; 13 from siblings and one from a matched-unrelated donor) were considered suitable for allogeneic BMT (Table 2). There were no exclusion criteria. Conditioning regimen comprised: busulphan (16 mg/kg) and cyclophosphamide (120 mg/kg) in four cases; and busulphan (7 mg/kg), cyclophosphamide (50 mg/kg) and total body irradiation (TBI; 12 Gy) in 10 cases. Melphalan (100 mg/m²) and TBI (12 Gy) was used for the second BMT in one patient (case 1; Table 2). Cyclosporine and methotrexate was used in all cases for graft-versus-host disease; AVN, avascular necrosis of hip.

Statistical analysis

Data were censored on the last day of 2001. For the whole group, actuarial survival was calculated by Kaplan–Meier analysis. Patients with or without

---

**Table 1.** Treatment and outcome of 54 patients with relapsed acute promyelocytic leukaemia

<table>
<thead>
<tr>
<th>Regimens</th>
<th>n</th>
<th>Early deaths</th>
<th>CR (%)</th>
<th>Second relapse, % (median time)</th>
<th>Outcome of further relapses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>19</td>
<td>53% (bleeding, sepsis)</td>
<td>47</td>
<td>22 (2/9) at 11 months and 21 months</td>
<td>Both died</td>
</tr>
<tr>
<td>BMT</td>
<td>14</td>
<td>36% (mucositis, sepsis)</td>
<td>64</td>
<td>11 (1/9) at 40 months</td>
<td>CR with second BMT</td>
</tr>
<tr>
<td>As₂O₃</td>
<td>21</td>
<td>-</td>
<td>100</td>
<td>38 (8/21) at 13 months</td>
<td>Two died, six in CR with As₂O₃ + ATRA</td>
</tr>
</tbody>
</table>

CR, complete remission; BMT, bone marrow transplantation; As₂O₃, arsenic trioxide; ATRA, all-trans retinoic acid.

**Table 2.** Outcome of 14 acute promyelocytic leukaemia patients treated with allogeneic bone marrow transplantation (BMT)

<table>
<thead>
<tr>
<th>Sex/age (years)</th>
<th>Time</th>
<th>Status</th>
<th>Conditioning</th>
<th>Engraftment</th>
<th>GvHD</th>
<th>OS</th>
<th>DFS</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Plt &gt;25</td>
<td>ANC &gt;1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 M/22</td>
<td>4.0</td>
<td>R1</td>
<td>BuCy</td>
<td>24</td>
<td>18</td>
<td>0</td>
<td>122.9+</td>
<td>Relapse, 2nd BMT done</td>
</tr>
<tr>
<td>2 F/22</td>
<td>20.4</td>
<td>CR2</td>
<td>BuCyTBI</td>
<td>20</td>
<td>19</td>
<td>2</td>
<td>55.7</td>
<td>Died of bronchiolitis obliterator</td>
</tr>
<tr>
<td>3 F/30</td>
<td>10.3</td>
<td>CR2</td>
<td>BuCyTBI</td>
<td>23</td>
<td>19</td>
<td>3</td>
<td>98.9+</td>
<td>cGvHD</td>
</tr>
<tr>
<td>4 F/14</td>
<td>17.9</td>
<td>CR2</td>
<td>BuCyTBI</td>
<td>13</td>
<td>17</td>
<td>2</td>
<td>93.5+</td>
<td>Hemorrhagic cystitis</td>
</tr>
<tr>
<td>5 M/39</td>
<td>20.1</td>
<td>R1</td>
<td>BuCyTBI</td>
<td>44</td>
<td>24</td>
<td>4</td>
<td>3.1</td>
<td>Died of sepsis</td>
</tr>
<tr>
<td>6 M/27</td>
<td>6.1</td>
<td>R1</td>
<td>BuCy</td>
<td>34</td>
<td>15</td>
<td>2</td>
<td>85.6+</td>
<td>AVN of hip</td>
</tr>
<tr>
<td>7 F/12</td>
<td>5.8</td>
<td>R1</td>
<td>BuCy</td>
<td>27</td>
<td>30</td>
<td>2</td>
<td>13.3</td>
<td>Died of sepsis</td>
</tr>
<tr>
<td>8 M/35</td>
<td>17.7</td>
<td>R1</td>
<td>BuCyTBI</td>
<td>24</td>
<td>20</td>
<td>2</td>
<td>6.2</td>
<td>Died of mucositis</td>
</tr>
<tr>
<td>9 M/32</td>
<td>46.1</td>
<td>CR2</td>
<td>BuCyTBI</td>
<td>27</td>
<td>19</td>
<td>2</td>
<td>7.2</td>
<td>Died of sepsis</td>
</tr>
<tr>
<td>10 F/45</td>
<td>16.6</td>
<td>CR2</td>
<td>BuCyTBI</td>
<td>20</td>
<td>24</td>
<td>4</td>
<td>1.4</td>
<td>Died of liver failure</td>
</tr>
<tr>
<td>11 F/14</td>
<td>22.1</td>
<td>CR2</td>
<td>BuCy</td>
<td>18</td>
<td>15</td>
<td>0</td>
<td>64.2+</td>
<td>Nil</td>
</tr>
<tr>
<td>12 M/45</td>
<td>22.1</td>
<td>CR2</td>
<td>BuCyTBI</td>
<td>14</td>
<td>15</td>
<td>2</td>
<td>9.7</td>
<td>Died of liver failure</td>
</tr>
<tr>
<td>13 F/47</td>
<td>15.7</td>
<td>CR2</td>
<td>BuCyTBI</td>
<td>28</td>
<td>25</td>
<td>2</td>
<td>3.7</td>
<td>Died of sepsis</td>
</tr>
<tr>
<td>14 F/35</td>
<td>19.0</td>
<td>CR2</td>
<td>BuCyTBI</td>
<td>13</td>
<td>18</td>
<td>2</td>
<td>45.5+</td>
<td>cGvHD, transient graft failure^</td>
</tr>
</tbody>
</table>

M, male; F, female; time, time from initial diagnosis to BMT in months; R, relapse; CR, complete remission; Bu, busulphan; Cy, cyclophosphamide; TBI, total body irradiation; Plt >25, days to platelet count >25 ×10⁹/l; ANC >1, days to absolute neutrophil count >1 ×10⁹/l; GvHD, acute graft-versus-host disease (grades 0–4); OS, overall survival in months; DFS, disease-free survival in months; +, survivor; cGvHD, chronic graft-versus-host disease; AVN, avascular necrosis of hip.

^One month of marrow aplasia with spontaneous recovery due to idiosyncratic hypersensitivity to azathioprine for GvHD.
maintenance therapy were compared by log-rank test. Overall survival (OS) was calculated from the day of diagnosis to the day of death or censorship. Disease-free survival (DFS) was calculated from the day of diagnosis to the day of confirmed marrow relapse. For salvage cases, analysis of OS was from the day of relapse to the day of death or censorship. The log-rank model was used to analyse differences in OS for the three different treatment methods for relapses (chemotherapy, BMT, As$_2$O$_3$-based treatment).

**Results**

**Treatment outcome of newly diagnosed APL**

A total of 153 patients were diagnosed with APL within the study period (Figure 1). Complete data for analysis were available in 143 patients. A total of 30 patients died before or during induction chemotherapy. CR1 was achieved in 113 cases. Relapses occurred in 54 patients, at a median of 13 months (range 5–96 months). Late relapses, defined as relapses occurring 2 years after CR1, occurred in 10 cases. The 5-year actuarial DFS from CR1 was 42%. This did not differ significantly for patients with ($n = 59$) and without ($n = 54$) maintenance therapy ($P = 0.087$), owing to the occurrence of more late relapses in the latter group (Figure 2).

**Treatment outcome of APL in first relapse**

The results of different treatment groups (chemotherapy alone, $n = 19$; chemotherapy followed by allogeneic BMT, $n = 14$; As$_2$O$_3$ followed by chemotherapy, $n = 21$) are shown in Table 1 and Figure 3. Ten patients treated with chemotherapy and five patients receiving BMT died from early treatment-related complications. Two patients receiving BMT died from late complications (hepatitis B virus-related liver failure and bronchiolitis obliterans) (Table 2). Durable CR2 was achieved in 30 cases.

**Treatment of APL in second or more advanced relapses**

There were 11 further relapses at a median of 11 months (range 8–48 months) (Table 1). Both patients in the chemotherapy group received further chemotherapy, and died from treatment-related complications. The only patient who relapsed again in the BMT group received a second allogeneic BMT from an HLA-identical sibling, and has remained in CR3. Two patients in the As$_2$O$_3$ group died before further treatment could be given. Six patients achieved and have remained in remission, with combined As$_2$O$_3$ plus ATRA therapy.

**Statistical analysis**

The 2-year actuarial OS from R1 leveled off at 23% for the chemotherapy group, 43% for the BMT group and 82% for the As$_2$O$_3$ group (Figure 3). As a result of efficient salvage of advanced relapses, the 5-year actuarial OS from CR1, at 68%, was much better than the DFS.
Discussion

With ATRA and chemotherapy as the induction regimen, the CR rate of 79% observed in this study is comparable to those of 72% and 96% reported previously [9]. However, our 5-year DFS, at 42%, was apparently inferior to the reported 3-year DFS of 86% to 90% in other series [10]. A number of reasons might account for this. One of the four centres in our study has not used maintenance therapy, which has been shown to be of beneficial effect in reducing relapses [11]. Furthermore, chemotherapy tolerance appears to be poor in Chinese people, and full-dose mercaptopurine maintenance was not achievable in most cases [12].

In relapsed APL, allogeneic BMT, chemotherapy and $\text{As}_2\text{O}_3$ are all useful treatment modalities, but the best choice and timing of treatment is as yet undefined [13]. Reported data on the use of ATRA plus chemotherapy for relapsed APL showed that only
29–35% of patients could be induced into durable remission [14, 15]. Allogeneic BMT for relapsed patients who achieved a second remission after ATRA plus chemotherapy also gave poor results. In one study, the leukaemia-free survival (LFS) was 22%, relapse rate (RR) was 54%, and the treatment-related mortality (TRM) was 40% [16]. In another study, only two of 11 APL patients in second remission survived the transplantation [17]. Data published by the European Blood and Marrow Transplantation (EBMT) Group showed that in 127 relapsed APL patients who received allogeneic BMT, the LFS was 53–61%, the RR was 10–22% and the TRM was 32–34% [18]. The data from the EBMT appeared to be slightly better than the former two studies, which could be related to different patient selection. However, these studies all showed that allogeneic BMT in APL patients in second remission was associated with a high TRM and an overall unsatisfactory outcome. As for As2O3, although a high remission rate can be achieved, the long-term follow-up results are less well defined. In two series comprising 87 relapsed cases, the 18- and 24-month LFS was 56% and 42%, respectively [19, 20].

In comparison with the studies of relapsed APL described above, our data offer a few advantages. This study involved a consecutive series, so that bias related to patient selection for various treatment options was diminished. This was particularly important for BMT, where patient selection could often affect the treatment outcome. Furthermore, the treatment and supportive care were similar. Our results might therefore give a better perspective on the relative merits of the different treatment options in relapsed APL.

We showed that with a follow-up of 3 years, treatment results for BMT were comparable to chemotherapy, but inferior to arsenic-based treatment for relapsed APL. The lower relapse rate with BMT was offset by the high early TRM, a phenomenon also observed in other studies [16–18]. Although few late relapses occurred after BMT, the survival curve remained unstable owing to late deaths from GvHD and organ toxicity. Furthermore, survivors after BMT might still suffer from the permanent side effects of immunosuppression, exposure to alkylating agents, infertility, premature menopause and increased risks of secondary malignancies. In contrast, As2O3-based therapy was associated with minimal toxicity or mortality. Although As2O3-induced second remissions were apparently associated with more subsequent relapses, long-term remission after combination therapy with As2O3 and ATRA might still be achieved in these patients [8]. Furthermore, the lack of organ damage meant that further relapses might still be salvaged by allogeneic BMT, although this was not required in any of our cases. Our results therefore suggest that As2O3-based therapy may be the treatment of choice for APL in first or more advanced relapses. For this reason, we have not performed BMT in any APL patients after 1997.

In conclusion, the availability of effective first-line and salvage therapy means that APL patients in any stage of their illness should be treated with curative intent, even when they have late advanced diseases [13]. As2O3 appears to be the best option for relapsed cases. The high efficacy of As2O3 in inducing second remissions means that optimal consolidation and maintenance of remission are key factors that will improve the cure rate. For allogeneic BMT to be offered as a consolidation, TRM must be improved. On the other hand, APL in advanced and repeated relapse appears to continue to respond to As2O3 treatment, which is associated with minimal side effects. Among these options, our data with short-term follow-up seemed to favour the use of repeated courses of As2O3. However, prospective clinical trials are needed to fully resolve the issue of As2O3 as compared with allogeneic BMT as the optimal treatment for relapsed APL.

Acknowledgements

This study was supported in part by the Kadoorie Charitable Foundation.

References


