Reduced medical costs and hospital days when using oral arsenic plus ATRA as the first-line treatment of acute promyelocytic leukemia

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\textbf{A B S T R A C T}

We have demonstrated that oral arsenic (Realgar-\textit{Indigo naturalis} formula, RIF) plus all-trans retinoic acid (ATRA) is not inferior to intravenous arsenic trioxide (ATO) plus ATRA as the first-line treatment of acute promyelocytic leukemia (APL). To compare the cost-effectiveness of oral and intravenous arsenic, we analyzed the results of 30 patients in each group involved in a randomized controlled trial at our center. The median total medical costs were $13,183.49 in the RIF group compared with $24,136.98 in the ATO group ($p<0.0001). This difference primarily resulted from the different costs of induction therapy ($p=0.016$) and maintenance treatment ($p<0.0001$). The length of hospitalization for the RIF group was significantly lower than that for the ATO group (24 vs. 31 days, $p=0.0001$) during induction therapy. During maintenance treatment, the estimated medical costs were $20,471.44 for each patient in the RIF group and $12,733.81 for each patient in the ATO group treated in an outpatient setting ($p<0.0001$). We conclude that oral RIF plus ATRA significantly reduced the medical costs and length of hospital stay during induction and remission therapy compared with ATO plus ATRA in APL patients.

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1. Introduction

Acute promyelocytic leukemia (APL) has transitioned from a highly fatal disease to a highly curable disease [1]. The chromosomal aberration (t(15;17) plays a central role in the development of APL and results in the formation of the fusion PML/RAR\textalpha. All-trans retinoic acid (ATRA), which targets RAR\textalpha proteins, and arsenic trioxide (ATO), which targets PML proteins, are two successful molecular-target drugs [3,4].

Recently, two randomized trials conducted by Lo-Coco et al. [5] and our group [6] provided strong evidence supporting first-line treatment with arsenic trioxide and all-trans retinoic acid (ATRA) for APL. ATRA and ATO have been adopted by the 2014 NCCN guidelines as the first-line treatment for APL [7], although arsenic resistance may develop in some patients [8]. However, ATO is costly and must be administered intravenously in a hospital setting. Therefore, the development of an orally active arsenic-containing formulation with comparable efficacy and side effects and lower costs is highly desirable. We recently demonstrated that oral arsenic, referred to as the Realgar-\textit{Indigo naturalis} formula (RIF), plus ATRA as a first-line treatment is not inferior to intravenous ATO plus ATRA in terms of 2-year disease-free survival (DFS) [6].

ATRA alone or combined with chemotherapy has been shown to reduce medical costs during APL remission induction therapy [9,10]. However, cost-effectiveness data of arsenic plus ATRA as the first-line treatment of APL are scarce. Therefore, we retrospectively analyzed the medical costs of the first-line treatment of arsenic and ATRA in APL patients involved in our prospective randomized controlled trial APL07 at Peking University People’s Hospital. We aimed to compare the medical costs and length of hospital stay between oral RIF plus ATRA and intravenous ATO plus ATRA as the first-line treatment of APL patients.

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2. Methods

2.1. Patients

The current study population consisted of 60 newly diagnosed APL patients who received the APL07 protocol at Peking University People’s Hospital from February 2008 through April 2011. Thirty patients received RIF plus ATRA and 30 patients received ATO plus ATRA as first-line treatment. All patients were between the ages of 15 and 60 years. The eligibility criteria included the following: diagnosis of de novo APL with the demonstration of the t (15;17) or PML/RAR rearrangement; white blood count (WBC) < 50 × 10⁹/L; adequate hepatic and renal reserves (defined as a total bilirubin, alanine aminotransferase, aspartate aminotransferase and creatinine < 2.0 times the institutional upper limit of the normal range); and a World Health Organization (WHO) performance status score of 2 or lower (on a scale of 0–4, where lower numbers indicate better performance). All participants signed an informed consent in accordance with the Declaration of Helsinki. This study was approved by the Ethical Committee of Peking University People’s Hospital, China. This study was registered with the Chinese Clinical Trial Registry (ChiCTR; ChiCTR-TRC-12002151).

2.2. Study design

The details of the clinical trial have previously been published [6]. In brief, the APL07 protocol was designed by the Chinese APL Cooperative Group as a randomized controlled trial. APL patients were randomized to receive the following induction therapies: oral RIF (60 mg/kg) or ATO (0.16 mg/kg). All patients, regardless of their induction group assignment, also received all-trans retinoic acid (25 mg/m²), ATO (10 mg/vial) was provided by the Harbin Yida Pharmaceutical Company, China, and RIF (270 mg/pill) was provided by the Anhui Tian Kang Pharmaceutical Company, China. RIF contained realgar (30 mg/pill), I. naturalis (125 mg/pill), Radix salviae miltiorrhizae (50 mg/pill), Radix pseudostellartiae (45 mg/pill) and garlic film (20 mg/pill). Mitoxantrone was added at a dose of 1.4 mg/m² per day for 5 days on the fourth day of the treatment, with the exception of the first day in the patients with a WBC count over 10 × 10⁹/L. The participants who achieved complete remission (CR) received three courses of the following consolidation chemotherapy: HA (homoharringtonine, 2 mg/m² for 7 days; cytarabine, 100 mg/m² for 5 days), DA (daunorubicin, 40 mg/m² for 3 days; cytarabine, 100 mg/m² for 5 days), and MA (mitoxantrone, 6 mg/m² for 3 days; cytarabine, 100 mg/m² for 5 days). The maintenance treatment included eight cycles that consisted of the sequential use of ATRA (25 mg/m² for 15 days for the first month) with oral RIF (60 mg/kg for 15 days for the second and third months for individuals who received oral RIF during induction) or ATO (0.16 mg/kg for 15 days for the second and third months for individuals who received ATO during induction) without cessation for two years. A flow chart illustrating the study design was included in our previous study [6].

2.3. Cost calculation

The direct medical costs for each patient were calculated, including the hospitalization costs of the induction therapy and three courses of the consolidation chemotherapy for inpatients and the estimated costs of the maintenance treatment for outpatients. All medical resource use related to APL treatment and its complications was collected and multiplied by the unit cost of each resource use. Non-medical costs that did not occur at the hospital were not considered.

The hospitalization costs of the induction therapy and consolidation chemotherapy were calculated based on the resource use derived from a computerized database at Peking University People’s Hospital. The database of the hospital’s information systems strictly adheres to the Medical Administration Regulations issued by the Beijing Municipal Commission of Development and Reform. All hospitalization costs were recorded according to the patient’s name/case number. The overall cost information and the component elements for each patient were collected from this database and double-checked and validated prior to analysis. The different elements of induction costs included the costs for medicine, blood products, lab tests, non-lab tests, hospital bed/daycare and other medical costs. The medicine included anti-leukemia drugs, antibiotics and other drugs for supportive care. The blood products included platelets, erythrocytes and plasma for transfusion.

The costs of maintenance treatment were estimated according to the direct medical resource use related to treatment because none of the patients were hospitalized during maintenance treatment. The patient dosage calculations were based on an average mass of 67 kg, and the costs of resource use were calculated based on the unit price set by the Beijing Municipal Commission of Development and Reform. The medical costs of maintenance treatment included the drug costs related to ATRA, arsenic, monitoring costs for minimal residual disease (MRD) and the costs for outpatient clinic transfusion, including the charges for peripherally inserted central venous catheters, which were used to provide reliable access for prolonged intravenous administration.

2.4. Statistical analysis

The costs were retrospectively calculated for the patients involved in a prospective randomized controlled trial and were compared in a post hoc analysis between 30 patients treated with oral RIF plus ATRA and 30 patients treated with ATO plus ATRA. Because the medical costs are slightly different among provinces in China, we chose patients from the same hospital to minimize patient selection bias. The Wilcoxon matched pairs test was used to compare the medical costs between the RIF and ATO groups. A probability level of < 0.05 was considered significant. All analyses were performed using SPSS 11.0.

2. Results

2.1. Patient characteristics

The current study included 60 patients at Peking University People’s Hospital; the data were analyzed as of April 2013. Sixty patients were included in the final analysis, with a median age of 35 years (range, 15–59 years). Patient characteristics are provided in Table 1. The patients in the ATO and RIF groups were not significantly different regarding any demographic feature or disease characteristic. The median follow-up time was 39 months (range, 24–64 months).

2.2. Overall medical costs

The data for the cost analyses were derived from 30 patients in the RIF group and 30 patients in the ATO group who were treated at Peking University People’s Hospital. Table 2 presents the overall medical costs incurred during APL treatment. The median total medical costs were $13183.49 in the RIF group compared with $24136.98 in the ATO group (p < 0.0001). This difference primarily resulted from the differential costs of induction (p = 0.016) and maintenance (p < 0.0001) treatments. The median total length of hospital stay in the RIF group was 48 days compared with 54 days in the ATO group (p < 0.0001). This significant difference was because of the reduction in the length of hospital stay during the induction phase. On average, the patients were hospitalized for 24 days in...
the RIF group and 31 days in the ATO group during the induction therapy.

2.3. In-hospital costs of the induction therapy

All charges accrued during the induction therapy were reviewed. These charges included medicine, blood products, lab tests, non-lab tests, hospital bed/daycare and other medical costs. The five categories (medicine, blood products, lab tests, non-lab tests, and hospital bed/daycare) accounted for 88.02% of the charges accrued by the RIF patients and 86.60% of the charges accrued by the ATO patients. The distributions of total costs were very similar between the two patient groups.

The average cost of induction therapy was $7232.86 for the RIF group, which was significantly lower than $9089.84 for the ATO group, primarily because of the lower costs of the medicine, hospital bed/daycare and other medical costs (Table 3). The costs of blood products were similar in the RIF and ATO groups ($1365.71 vs. $1257.30, respectively, \( p = 0.78 \)) during induction therapy. No significant differences in the costs of the lab or non-lab tests were identified between the two groups. In addition, the other medical costs for the ATO group were significantly higher than those in the RIF group. The longer duration of hospitalization and greater consumption of materials related to the infusion of ATO may explain this discrepancy.
Table 3
Costs of the induction therapy.

<table>
<thead>
<tr>
<th>RIF group</th>
<th>Cost (Dollar)</th>
<th>(%)</th>
<th>ATO group</th>
<th>Cost (Dollar)</th>
<th>(%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicine</td>
<td>3630.95 (977.14–8959.21)</td>
<td>50.20%</td>
<td>5026.51 (2200.95–9823.17)</td>
<td>55.30%</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>Blood products</td>
<td>1365.71 (0–3800.00)</td>
<td>18.88%</td>
<td>1257.30 (0–4139.68)</td>
<td>13.83%</td>
<td>0.78</td>
<td></td>
</tr>
<tr>
<td>Lab tests</td>
<td>1137.46 (374.44–2391.90)</td>
<td>15.73%</td>
<td>1265.71 (472.70–2899.84)</td>
<td>13.93%</td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td>Non-lab tests</td>
<td>91.27 (0–275.56)</td>
<td>1.26%</td>
<td>110.79 (0–438.73)</td>
<td>1.22%</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>Hospital bed/daycare</td>
<td>147.84 (66.67–214.76)</td>
<td>2.04%</td>
<td>211.59 (127.84–425.08)</td>
<td>2.33%</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>All other medical costs</td>
<td>859.68 (230.00–1694.76)</td>
<td>11.89%</td>
<td>1217.94 (414.44–3767.62)</td>
<td>13.40%</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Total costs</td>
<td>7232.86 (3009.37–13498.41)</td>
<td>100%</td>
<td>9089.84 (5326.67–15631.90)</td>
<td>100%</td>
<td>0.016</td>
<td></td>
</tr>
</tbody>
</table>

RIF: Realgar-Indigo naturalis formula; ATO: arsenic trioxide.

Table 4
Drug and blood product usage during the induction therapy.

<table>
<thead>
<tr>
<th>RIF group</th>
<th>ATO group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costs of antibiotics (Dollar)</td>
<td>1998.10 (0.48–6770.00)</td>
<td>2255.71 (0.5–5769.37)</td>
</tr>
<tr>
<td>Costs of anti-leukemia drugs (Dollar)</td>
<td>182.86 (73.81–348.89)</td>
<td>686.30 (194.76–1265.71)</td>
</tr>
<tr>
<td>costs of other drugs (Dollar)</td>
<td>1439.05 (643.02–2769.05)</td>
<td>2083.57 (509.52–4507.14)</td>
</tr>
<tr>
<td>Amount of platelet transusion (unit)</td>
<td>1034 (0–16)</td>
<td>1000 (0–3000)</td>
</tr>
<tr>
<td>Amount of erythrocyte transusion (unit)</td>
<td>569 (0–1600)</td>
<td>708 (0–1400)</td>
</tr>
<tr>
<td>Amount of plasma transusion (ml)</td>
<td>966 (0–3400)</td>
<td>1431 (0–6400)</td>
</tr>
</tbody>
</table>

RIF: Realgar-Indigo naturalis formula; ATO: arsenic trioxide.

Table 5
Mean estimated costs for each patient during maintenance treatment.

<table>
<thead>
<tr>
<th>RIF group</th>
<th>ATO group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated costs of ATRA (Dollar)</td>
<td>110.95</td>
<td>110.95</td>
</tr>
<tr>
<td>Estimated costs of arsenic (Dollar)</td>
<td>960</td>
<td>6080</td>
</tr>
<tr>
<td>Estimated costs of transusion (Dollar)</td>
<td>396</td>
<td>4106.67</td>
</tr>
<tr>
<td>Estimated costs of MRD monitoring (Dollar)</td>
<td>796.19</td>
<td>796.19</td>
</tr>
<tr>
<td>Estimated total costs (Dollar)</td>
<td>2047.14</td>
<td>11273.81</td>
</tr>
</tbody>
</table>

RIF: Realgar-Indigo naturalis formula; ATO: arsenic trioxide; MRD: minimal residual disease.

As shown in Table 4, the costs of anti-leukemia drugs were significantly lower for the RIF compared with the ATO group (p < 0.001) because of the lower cost of RIF compared to ATO in the induction therapy; this explains, in part, the difference in medicine costs observed between the two groups. There was a significant difference in the costs of the other drugs for supportive care between the two groups, which may have been a result of the different lengths of hospital stay. The costs of antibiotics were not significantly different between the two groups. No significant differences in the costs of platelet, erythrocyte and plasma transfusions were identified between the two groups.

2.4. In-hospital costs of consolidation chemotherapy

The median medical costs of first, second and third courses of consolidation were $1450.79, $1310.95, and $1411.75, respectively, for the RIF group and $1452.43, $1294.44, and $1026.35, respectively, for the ATO group (Table 1). Because the chemotherapy protocols were similar, the costs of the three cycles of consolidation chemotherapy were also similar for the RIF and ATO groups (p = 0.99, p = 0.95, and p = 0.3, respectively). Furthermore, there was no difference between the RIF and ATO groups regarding the length of hospitalization during consolidation chemotherapy (p = 0.65, p = 0.95, and p = 0.85, respectively).

2.5. Estimated outpatient clinic costs for the maintenance treatment

During maintenance treatment, the patients in the RIF group were treated at home, while the patients in the ATO group were treated in an outpatient setting. As shown in Table 5, the estimated costs of maintenance treatment for each patient differed according to the preceding treatment. The estimated maintenance costs for each patient were $2047.14 in the RIF group compared with $11,273.81 in the ATO group (p < 0.0001). The higher maintenance costs in the ATO group are a result of the higher cost of ATO and the direct medical costs caused by the ATO infusion in the outpatient clinic. The extra expenses for each patient in the ATO group were $4106.67 and were a result of the ATO infusions during the maintenance treatment, which did not occur in the RIF group.

3. Discussion

Recent clinical trials have demonstrated that high CR rates and DFS can be achieved using a combination of ATRA and ATO as a first-line treatment for newly diagnosed APL [4–6,11–13]. Moreover, the GIMEMA group demonstrated broadly better quality of life (QoL) outcomes post-induction, favoring patients treated with intravenous ATO versus those who received standard chemotherapy [14]. The study further supported the use of ATRA plus ATO as the preferred first-line treatment in patients with low- or intermediate-risk APL. Oral active arsenic, such as As4S4 as a single drug or in a formula (e.g., RIF), has also demonstrated clear efficacy and good safety [15–17]. Oral RIF, which is commercialized and commonly available in China, was used in place of ATO as a first-line treatment in our previous study. 6 Compared to intravenous ATO, RIF is relatively inexpensive and can be administered orally in outpatients. Thus, oral RIF may decrease the medical costs associated with APL treatment.
To our knowledge, ours is the first study to compare the medical costs between oral RIF plus ATRA and intravenous ATO plus ATRA as the first-line treatment for APL patients. Furthermore, our analyses of medical costs were based on the actual expenses of APL patients rather than the estimation of costs based on the resource use obtained from study case reports of induction and consolidation treatment. Thus, the results of the current study provide new, real-world information regarding the comparative costs of oral RIF plus ATRA versus intravenous ATO plus ATRA. Our results demonstrated that the medical costs of induction and the entire treatment course in the RIF group were significantly lower than in the ATO group. The main cause of this cost difference may be the lower number of hospitalization days and the lower costs of RIF compared with ATO during the induction therapy. During induction, the main reason for the long in-hospital stay was that the patients in the ATO group had to remain in the hospital for intravenous ATO, while the patients in the RIF group could receive oral RIF as outpatients to avoid infections and bleeding when blood counts recovered. In general, the in-hospital stay was the major cost driver in the treatment of APL [18]. The reduced in-hospital stay greatly contributed to the lower medical costs during induction therapy. Nevertheless, our study demonstrated that the shorter in-hospital stay had no negative impact on the CR or DFS rates.

During the maintenance phase, the direct medical costs of the ATO group, which included the incremental costs incurred by outpatient infusion of ATO and the higher cost of arsenic, were significantly increased compared with the RIF group. Furthermore, substantial attention should be paid to the indirect costs caused by outpatient administration of ATO, which are of importance from a societal point of view [19]. However, most patients in the RIF group could resume their work or study status with a relatively better quality of life during maintenance therapy after completing three cycles of consolidation chemotherapy.

Recently, Lachaine et al. first demonstrated that ATRA plus ATO is a cost-effective strategy compared with ATRA plus chemotherapy for the treatment of patients with newly diagnosed APL in Canada [20]. This group also drew the same conclusion when comparing ATO to ATRA plus chemotherapy in relapsed/refractory APL in Canada [21]. However, these studies used a time-dependent Markov model-based analysis rather than real medical costs, and many assumptions were made due to very limited data, which may increase the uncertainty of the results. Therefore, these results should be confirmed by other groups using actual medical costs. Our study showed the relatively low medical costs ($13,183.49–24,136.98) using ATRA plus arsenic as first-line treatment of APL based on actual medical costs rather than a model-based analysis. Because the significantly different costs of drugs between Canada and China (ATO: CAD$530.00/10 mg ampule in Canada, ¥160 ($CAD$26.7)/10 mg ampule in China) and the commercial unavailability of oral arsenic outside of China, it was difficult to compare the results of our study to those of the Canadian study. However, both studies supported using ATRA and ATO as first-line treatment from an economic point of view.

Because the medical costs differ slightly among different provinces in China, we selected patients from the same hospital to minimize patient selection bias. The Beijing Municipal Commission of Development and Reform issues a book for the Medical Administration Regulation to guide medication prices and hospital costs, including hospital daycare and professional fees. Thus, the medical costs of patients who receive the same treatment should be equal in the same province. It is true that there are differences in the costs of antibiotics that are chosen by different physicians because the usage of antibiotics was not standardized in the protocols. However, this difference could be minimized when many patients involved in a randomized controlled trial are analyzed.

There are several limitations to this study. First, this cost analysis was conducted on the data from one hospital. Additional analyses using a larger number of cases from multiple hospitals may generate more relevant results. Second, our results were based on the cost analyses of a therapy protocol from China. Because of the differences in medical practice and health care system organizations, it is unknown whether the results can be accurately extrapolated to other countries. Third, the maintenance costs were calculated based on the treatment procedure and patient follow-up. More robust results will be obtained if the real-world costs of maintenance therapy are calculated, including the evaluation of the quality of life related to the treatments and the indirect costs, such as time off work and lost productivity.

Based on our cost analysis, compared with intravenous ATO, oral RIF achieves comparable remission and survival outcomes at a lower cost and with a shorter hospital stay when used as the first-line treatment for APL patients. Moreover, our pilot study including 20 patients further showed that oral arsenic and ATRA without chemotherapy as first-line treatment of non-high-risk APL could achieve 100% CR and PML-RARA-negative, with low medical costs and potential quality of life benefits [22]. Therefore, we recommend consideration of RIF as the preferred first-line APL therapy in the design of medical policies. We are confident that this treatment approach will benefit not only the patients, with a reduced length of hospital stay, as well as the payers and the care delivery system, considering the significant cost savings.

Conflict of interest

The authors declare there is no conflict of interest.

Author contribution

H.-H.Z., G.-W.L, H.J, Q.I designed the study; G.-W.L, H.J, S.H, L.-W. S. collected and assembled the data; H.-H.Z. G.-W. L, H J wrote the manuscript; and all authors gave final approval for the manuscript. H.J and G.-W.L contributed equally to this work.

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References


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