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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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ABSTRACT

We have demonstrated that oral arsenic (Realgar-*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 $24136.98 in the ATO group ($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 $2047.14 for each patient in the RIF group treated at home compared with $11273.81 for each patient in the ATO group treated in an outpatient setting ($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/RARα [2]. All-trans retinoic acid (ATRA), which targets RARα 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-*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 scare. 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) $<50 \times 10^9$/L; adequate hepatic and renal reserves (defined as a total bilirubin, alanine aminotransferase, aspartate aminotransferase and creatinine $\leq$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/m^2). 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 pseudostellariae* (45 mg/pill) and garment film (20 mg/pill). Mitoxantrone was added at a dose of 1.4 mg/m^2 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 10×10^9/L. The participants who achieved complete remission (CR) received three courses of the following consolidation chemotherapy: HA (homoharringtonine, 2 mg/m^2 for 7 days; cytarabine, 100 mg/m2 for 5 days), DA (daunorubicin, 40 mg/m^2 for 3 days; cytarabine, 100 mg/m2 for 5 days), and MA (mitoxantrone, 6 mg/m^2 for 3 days; cytarabine, 100 mg/m^2 for 5 days). The maintenance treatment included eight cycles that consisted of the sequential use of ATRA (25 mg/m^2 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

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