Cost-Effectiveness Study Comparing Imatinib with Interferon-α for Patients with Newly Diagnosed Chronic-Phase (CP) Chronic Myeloid Leukemia (CML) from the Chinese Public Health-Care System Perspective (CPHSP)

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ABSTRACT

Objective: Imatinib, a breakthrough oral molecular-targeted therapy, has demonstrated durable responses and significant survival advantage compared with interferon-based treatment. This study compares imatinib with interferon in newly diagnosed chronic-phase chronic myeloid leukemia (CML-CP) patients from the Chinese public health-care system perspective (CPHSP).

Methods: One-year cost responder and lifetime cost-utility analyses were conducted, respectively. Complete cytogenetic response was used to define a responder. Direct medical costs were included. Response rates as well as survival estimates were obtained from published literature.

Results: The cost per responder for interferon was close to 20 times higher than that for imatinib. The cost per additional responder was RMB36,545. The incremental cost-effectiveness ratio (ICER) comparing imatinib with interferon was RMB73,674 (95% confidence interval RMB67,712–RMB79,637) per quality-adjusted life-year.

Conclusion: In newly diagnosed CML-CP, the cost per responder for patients treated with imatinib is much lower than that for patients treated with interferon. In the cost-utility analysis, the ICER is below the cost-effectiveness threshold recommended by the World Health Organization for developing countries. Therefore, imatinib is more cost-effective than interferon from the CPHSP.

Keywords: China, CML, cost-effectiveness, imatinib.

Introduction

Chronic myeloid leukemia (CML) is a rare disease, with an estimated 4570 new cases diagnosed in 2007 in the United States, among 44,240 new cases of leukemia projected overall [1]. CML represents nearly 13% to 14% of leukemias, and an estimated 20% of leukemias in adults [2,3]. There is no published CML incidence data for China yet. Some local data indicate that the CML incidence for China may be much lower, less than 1 per 100,000 per year. The median age of disease onset is 67 years old, however, CML occurs in all age groups. Clinically, CML progresses through three distinct phases of increasing severity and refractoriness to therapy, namely, chronic phase (CP), accelerated phase (AP), and blast crisis (BC) [2]. The majority of patients (90%) is diagnosed in the CP upon presentation of disease [4]. Phase duration and survival shorten as patients progress through the AP and BC. Untreated CML progresses from a CP to a rapidly fatal blast phase, generally over 3 to 5 years [5]. The blast phase is often preceded by a transition period, AP.

Understanding the pathogenesis of the disease began with the discovery of the Philadelphia (Ph) chromosome followed by appreciation of its molecular counterpart, the BCR–ABL fusion gene [5,6]. Recognition of the tyrosine kinase (TK) activity of the BCR–ABL proteins led to the discovery of imatinib. The introduction of imatinib has resulted in a revolutionary step in the management of CML and a shift in paradigm for the management of cancer in general [7].

Imatinib (Glivec, Novartis, Basel, Switzerland) is an oral TK inhibitor indicated for the treatment of Ph chromosome-positive CML in all phases. Imatinib has become the standard of care and is recommended by the US National Comprehensive Cancer Network as the first-line therapy for newly diagnosed CML-CP patients. Interferon or allogeneic stem cell transplantation should no longer be considered as initial therapy for CML-CP [8]. Furthermore, imatinib was recommended to be the preferred initial treatment by an international expert panel [7].

In China, imatinib is recommended as first-line treatment in CML-CP. Nevertheless, many patients were still treated with interferon as first-line treatment or went on to bone marrow transplant (BMT) because both interferon and BMT are widely reimbursable, whereas imatinib is only reimbursable in a limited number of cities with high reimbursement barriers. This study compares the cost-effectiveness between imatinib and interferon from the Chinese public health-care system perspective (CPHSP). We hope that the results could supplement Chinese payers in the decision on which treatment should be reimbursed for CML-CP patients.

A number of imatinib cost-effectiveness studies in CML have been published for the United States [9] and UK [10] as well as China [11]. Nevertheless, all studies were based on short-term (less than 2 years) clinical data. Two recent publications using imatinib 5-year follow-up data demonstrated that imatinib was more cost-effective than interferon in treating CML-CP from the US [12] and Brazil [13] payers’ perspective, respectively. This study used the survival data from Reed et al. [12] to compare imatinib with interferon from the CPHSP.
Methods

Two cost-effectiveness analyses were conducted to compare imatinib with interferon in newly diagnosed CML-CP patients. Interferon monotherapy was used because in China, interferon is usually used as a monotherapy. Newly diagnosed patients were defined as patients who were diagnosed with CML-CP and have not been treated or have been minimally pretreated with hydroxyurea.

Cost Responder

Complete cytogenetic response (CCyR) is associated with long-term survival in CML and is an effective measure for treatment efficacy [14–18] (for details of References 14–26, see Cost-Effectiveness Study Comparing Imatinib with Interferon-α for Patients with Newly Diagnosed Chronic-Phase (CP) Chronic Myeloid Leukemia (CML) from the Chinese Public Health-Care System Perspective (CPHSP) Value in Health Supporting Information, part VI at: http://www.ispor.org/Publications/value/ViH12s3_Feng.asp). Furthermore, the European Leukemia Net (ELN) defined CCyR at 12 months after diagnosis as an optimal response [19]. If a patient achieved a CCyR at 12 months, the patient is defined as a responder; otherwise, the patient is a nonresponder. This study did not compare CCyR at 18 months because of the following reasons: CCyR is not available for patients treated with interferon monotherapy; and the CCyR from O’Brien’s [20] study was for patients treated with interferon in combination with cytarabine. The cost per responder at 12 months was calculated by dividing the 12-month cost of treatment by the CCyR rate. The cost per additional responder was calculated by dividing the difference in costs (imatinib minus interferon) by the difference in response rate. The 12-month cost of treatment consists of the direct medical costs that occurred during the first year of treatment: drug cost, office visits, and blood/lab tests. Hospitalization costs were not included as few patients require hospitalization during the CP [9]. Treatment costs to manage adverse events (AEs) were not included as data were unavailable for China. Patients treated with imatinib will incur significantly less side effects than those treated with interferon [20]. By excluding the treatment costs managing AEs, we underestimated the cost savings from AEs for imatinib.

Data

The CCyR at 12 months for imatinib was obtained from the International Randomized Interferon versus STI571 (IRIS) study [21], whereas the CCyR for interferon was from Baccarani et al. [22]. No published data were available for imatinib CCyR for China patients; therefore, we used the published IRIS data. Regarding CCyR for interferon, the only published China data showed that CCyR at 19 months for interferon used in combination with hydroxyurea and cytarabine was 3.2% [23]. The CCyR for interferon from the IRIS study was not used because that is for interferon combined with cytarabine. Additionally, over half of the interferon arm patients crossed over to imatinib after 19 months. Therefore, CCyR for interferon from Baccarani et al. [22] was used. The patient populations from the IRIS and Baccarani et al. [22] studies were similar, with both containing newly diagnosed CML-CP patients who had not been treated or had been minimally pretreated with hydroxyurea. Price information on drugs was obtained from the listed retail price in China. The price for interferon was based on imported interferon as the qualities and prices for domestic-made interferon vary widely.

More importantly, to our knowledge, there is no publication on treatment outcomes, such as cytogenetic response, for domestic-made interferon. Unit costs on office visit and blood test were estimated based on the average fees charged by top tier hospitals in China (Table S1). For more details, see Cost-Effectiveness Study Comparing Imatinib with Interferon-α for Patients with Newly Diagnosed Chronic-Phase (CP) Chronic Myeloid Leukemia (CML) from the Chinese Public Health-Care System Perspective (CPHSP) Value in Health Supporting Information, part II at: http://www.ispor.org/Publications/value/ViH12s3_Feng.asp.

Cost-Utility Analysis

Model Structure

The framework of the lifetime cost-utility analysis is presented in Figure S1 (for details, see Cost-Effectiveness Study Comparing Imatinib with Interferon-α for Patients with Newly Diagnosed Chronic-Phase (CP) Chronic Myeloid Leukemia (CML) from the Chinese Public Health-Care System Perspective (CPHSP) Value in Health Supporting Information, part I at: http://www.ispor.org/Publications/value/ViH12s3_Feng.asp). In this analysis, CML-CP patients who received interferon first, imatinib will not be a treatment option. Similarly, with CML-CP patients who received imatinib first, interferon will not be a treatment option. This will allow us to have a clean comparison between imatinib and interferon. For patients who progressed into advanced phases, we assigned the same time in AP and BC, and the same utility weights and estimates of resource use for both treatment groups. The time in each disease phase determines the life-years (LYs). The total LYs for both treatment groups were obtained from Reed et al. [12]. Time in advanced phases was assumed to be the same for both treatment groups, with 10 months in AP and 13 months in BC phase [9]. Adjusting the duration in each disease phase by the appropriate utility weight determines the quality-adjusted LY (QALYs). Drug costs as well as other treatment costs incurred during all disease phases determine the total costs with each treatment choice (imatinib or interferon). In the cost-utility analysis, the direct medical costs for CP included the same resources as the costs in the cost responder analysis, where hospitalizations and costs managing AEs were not included. Nevertheless, the direct medical costs for advanced phases included hospitalizations. Based on the total cost and health outcomes, the incremental cost-effectiveness ratio (ICER) can be computed.

Data

This study applied the lifetime survival data for imatinib and interferon from Reed et al. [12]. The Reed et al. [12] study used the 60-month data from the IRIS trial to extrapolate and estimate the lifetime survival for imatinib. Because 58% of patients randomized to receive interferon had crossed over to imatinib after 19 months [20], historical data from the literature were used to estimate the lifetime survival for interferon [18,22]. In China, the Global Imatinib Patient Assistance Program (GIPAP) has been available since 2003, where many CML patients have been treated with imatinib for 3 years. The 5-year survival was 91% for CML patients receiving 400 mg/day in the GIPAP (data on file), similar to the 5-year survival rate (89%) for CML-CP patients treated with imatinib from the IRIS trial. Because this GIPAP data are not published and there is no published lifetime survival data for interferon in China, we used the published Reed et al. [12] lifetime survival estimate for both imatinib and interferon. Utility weights for CP and advanced phases were based on...
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the Reed et al. [9] study, where utility weights were derived from the EuroQol EQ-5D (a standardized instrument for use as a measure of health outcome) collected in the IRIS trial.

Only direct medical costs were included. Treatment costs were estimated based on treatment protocols from the top tier hospitals in China. Unit price, administrative dose, as well as frequency of resource use are presented in Table S1. All costs and outcomes were discounted at a rate of 3.5% per annum following the UK Health Technology Assessment recommendation in the base-case scenario because there is no consensus on which discount rate to use.

Results

Cost-Responder

In the base-case analysis, the dosage for interferon was 3 MIU per day, reflecting the practice in China. Nevertheless, the CCyR at 12 months for interferon was based on the interferon dosage of 3 MIU per day from Baccarani et al. [22]. Therefore, a sensitivity analysis was conducted for interferon 5 MIU per day. The 12-month cost of treatment associated with imatinib is 20% higher than interferon; however, the CCyR rate for imatinib is 23 times better than that for interferon. Cost per responder for interferon at 3 MIU per day is 19 times higher than that for imatinib, whereas for interferon at 5 MIU per day, it is about 28 times higher than that for imatinib. The cost per additional responder is RMB36,545, comparing imatinib with interferon at 3 MIU per day. Imatinib dominates interferon at 5 MIU per day in cost per additional responder (for details, see Cost-Effectiveness Study Comparing Imatinib with Interferon-α for Patients with Newly Diagnosed Chronic-Phase (CP) Chronic Myeloid Leukemia (CML) from the Chinese Public Health-Care System Perspective (CPHSP) Value in Health Supporting Information, Part III at: http://www.ispor.org/Publications/value/ ViHsupplementary/ViH12s3_Feng.asp).

Cost-Utility

In the base-case analysis (for details, see Cost-Effectiveness Study Comparing Imatinib with Interferon-α for Patients with Newly Diagnosed Chronic-Phase (CP) Chronic Myeloid Leukemia (CML) from the Chinese Public Health-Care System Perspective (CPHSP) Value in Health Supporting Information, Part IV at: http://www.ispor.org/Publications/value/ ViHsupplementary/ ViH12s3_Feng.asp), patients receiving interferon were estimated to live an average of 19 years compared with 9 years for patients receiving interferon, an incremental gain of 10 years. Adjusting for quality of life, the incremental gain was 9.5 QALYs. Applying a 3.5% discount rate, the incremental gain in survival was 6.3 years and 6.4 QALYs. Discounted lifetime costs were RMB473,096 higher among patients receiving interferon. Combining the estimates in QALYs and lifetime costs, the ICERs were RMB74,908 per LY gained and RMB73,679 per QALY. The upper limits for both ICERs were around RMB80,000. Two one-way sensitivity analyses were conducted (for details, see Cost-Effectiveness Study Comparing Imatinib with Interferon-α for Patients with Newly Diagnosed Chronic-Phase (CP) Chronic Myeloid Leukemia (CML) from the Chinese Public Health-Care System Perspective (CPHSP) Value in Health Supporting Information, Part V at: http://www.ispor.org/Publications/value/ ViHsupplementary/ViH12s3_Feng.asp). The higher the discount rate, the lower the ICER, hence, more favorable for imatinib. Another sensitivity analysis was conducted for imatinib unit price at the highest listed retail price (6% increase over the base-case imatinib price) and the usual retail price (4% discount of the base-case imatinib price). Both sensitivity analyses indicate that the ICER is sensitive to the discount rate and the imatinib price.

Conclusion and Discussion

The cost per responder for interferon is higher than that for imatinib, and the cost per additional responder is RMB36,545. Furthermore, the cost-utility analysis shows the ICERs of RMB74,908 per LY gained and RMB73,679 per QALY comparing favorably with the World Health Organization recommended cost-effectiveness threshold as three times the GDP per capita for developing countries [24,25].

Wang et al. [11] found the cost-effectiveness ratio to be RMB156,000 per QALY, about twice as much compared with this study. It used the IRS study with 20-month follow-up, whereas this study used Reed et al.’s [12] study where the IRS study with 60-month follow-up was used. Using 60 months versus 20 months follow-up, imatinib demonstrated more survival advantage over interferon [12]. In addition, this study incorporated the GIPAP scheme (the current practice in China) to estimate the imatinib cost, which reflected about half of that used in Wang et al. [11].

Some limitations of the study need to be considered. It is assumed that no price cut throughout the lifetime for imatinib or interferon. In practice in China, once a product is listed on the national reimbursement drug list, it faces a price cut every year in the range of 2% to 10%. Therefore, we may have underestimated the cost-effectiveness of imatinib. In both cost responder and cost-utility analyses, treatment costs to manage AEs were not included because in China, such data were difficult to collect. We expect that if we include the AE treatment costs, the results would be more favorable for imatinib as patients treated with imatinib require much less AEs management than those treated with interferon [22]. Because of the durable responses and survival benefit of imatinib, 86% of the patients treated with imatinib in the IRS study are alive after 7 years of follow-up [26]. Therefore, lifetime costs and survival for imatinib had to be estimated and extrapolated based on available data. As longer term data become available, it will be important to reevaluate the cost-effectiveness if, by then, sufficient mortality events become available. In addition, this study used the published estimated survival for imatinib and interferon, as patient-level data with detailed clinical information were unavailable in China yet.

Imatinib has changed the natural history of CML by improving survival and transforming CML from a life-threatening to a chronic disease. This breakthrough medicine is recommended globally as the standard first-line treatment [8,21]. Not only is it effective, but also, it has been demonstrated to be cost-effective in many jurisdictions [9–13]. This study confirms that imatinib is cost-effective than interferon-α from the CPHSP.

This study has been presented at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 3rd Asia-Pacific Conference and the Chinese Society for Pharmacoeconomics and Outcomes Research inauguration, respectively, in 2008. Comments from the audience as well as from the four reviewers are greatly appreciated.

Source of financial support: None. Zi Chen, Chun Wang, Xiaoping Xu, and Weiwei Feng have no conflicts to declare.

References