Cost-effectiveness analysis of transplantation-ineligible elderly acute leukemia harboring molecular target; Ph-positive acute leukemia and FLT3 mutated acute myeloid leukemia

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Research Article

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Abstract

Objective: Tyrosine kinase inhibitors (TKIs) and FLT3 inhibitors are promising agents for Ph-positive acute leukemia (Ph⁺ AL) and FLT3 mutated acute myeloid leukemia (FLT3-AML), respectively. We examined the cost-effectiveness ratio (CER) of dasatinib and ponatinib for Ph⁺ AL and the cost-effectiveness of gilteritinib and quizartinib for FLT3-AML in elderly. Molecular therapy can fit elderly population rather than chemotherapy (CT).

Results: The daily drug cost of drug dasatinib, ponatinib, gilteritinib, and quizartinib is $240, $170, $524, and $479 in terms of treatment maintenance dose, respectively. When treated with SCT, CT, dasatinib, and ponatinib in Ph⁺ AL, the CERs were $322,375, $34,928, $61,104, and $46,234, respectively. The CERs for FLT3-AML treated with SCT, CT, gilteritinib, and quizartinib were $355,270, $42,717, $94,987, and $90,080, respectively. The treatments with TKIs and FLT3 inhibitors in elderly remained expensive and inferior than conventional CT, however, the cost-effectiveness ratio was superior compared to that with SCT. Although TKIs and FLT3 inhibitors have a higher drug cost than conventional CT, their promising survival benefit can offset the cost. TKI or FLT3 inhibitor monotherapy is recommended for elderly patients with Ph⁺ AL or FLT3-AML, such as situationally unfit elderly and even for relapse and refractory cases post-SCT recurrence.

1. Introduction

Various therapeutic target molecules have been discovered in hematological malignancies. The most representative case is BCR-ABL1 translocation (Philadelphia chromosome) -positive acute leukemia (Ph⁺ AL), tyrosine kinase inhibitors (TKI) [1]. We are now in an era where long-term prognosis is expected even for elderly people with the administration of TKI [2,3]. Similarly, a specific molecular-targeted therapeutic agent for FMS-like tyrosine kinase 3 (FLT3) mutated acute myeloid leukemia (FLT3-AML), FLT3 inhibitor, is used to induce remission before hematopoietic stem cell transplantation (SCT) for relapsed/refractory AML [4,5]. It has been developed as an effective therapeutic drug and is expected to improve the prognosis even for elderly people who are not indicated for SCT. Moreover, for vulnerable elderly population, molecular target therapy by using TKI or FLT3 inhibitor exert longer survival rather than cytotoxic chemotherapy (CT).

2. Main Text

We examined the cost-effectiveness of dasatinib (D)[2] and ponatinib (P)[3] for Ph⁺ ALL and the cost-effectiveness of gilteritinib (G)[4] and quizartinib (Q)[5] for FLT3-AML, compared to SCT [6–8] or CT [9]. For medical cost analysis, the cost-effectiveness ratio (CER) was evaluated as for estimated overall survival according to each clinical evidence [2–9]. Considering the annual discount rate of 3%. A Markov decision model was adapted, and the CER was calculated where as if a patient treatment was select any in four branches (SCT, CT, drug 1, and drug 2), as for overall survival from the decision point for each disease. The transplantation cost was calculated based on the previous reports [10]. The medical cost of
each drug is the dosage stated in the package insert, and the domestic drug price in 2020 is used. Survival time after SCT and survival time after treatment with each drug were fitted with the results of updated and consensus comparative studies. For convenience, the cost-effectiveness was calculated using the survival time up to 1 year after treatment, and the results are described in CER per patient per year. The currency conversion was converted from 1 US dollar to 113 Japanese yen. No sensitivity analysis or Monte Carlo simulation was performed. The daily drug cost of drug D / P / G / Q is $240 / $170 / $524 / $479 in terms of treatment maintenance dose, respectively. When treated with SCT / CT / D / P in Ph⁺ AL, the CERs were $322,375 / $34,928 / $61,104 / $46,234, respectively (Fig. 1a). The CERs for FLT3-AML treated with SCT / CT / G / Q were $355,270 / $42,717 / $94,987 / $90,080, respectively (Fig. 1b).

The CERs of FLT3 inhibitor for FLT3-AML is higher than that of CT treatment for the same disease due to the high daily drug cost, but the median survival time when using the drug G / Q is 9.3 / 6.2 months, respectively. In addition, the CERs with molecular therapies (TKIs and FLT3) for each disease were comparable. Treatment with FLT3 inhibitors in elderly remained expensive in terms of proper health economy as defined by the World Health Organization (WHO) and the National Institute for Health and Care Excellence (NICE). The total cost of molecular therapies is not so high compared with that of SCT. The use of TKIs for Ph⁺ AL is cost effective [11–13] but that of the FLT3 inhibitor for FLT3-AML is still rare [14]. TKIs, including imatinib and second [11] to third [12] generation TKI agents, exert acceptable cost-effectiveness for Ph⁺ AL. Our results showed that molecular target therapy was effective compared with conventional chemotherapy with TKIs and FLT3 inhibitors. Thus, patients with acute leukemia, especially the elderly, harboring the target molecule should receive less intensive molecular target therapy when they are ineligible for intensive chemotherapy. Nowadays, TKI availability has improved the prognosis of Ph⁺ ALL rather than Ph⁻ ALL in older patients [13]. This benefit must be theoretically compared between AML cases with/without FLT3 mutation.

Pandya et al. reported the cost-effectiveness of gilteritinib for relapsed or refractory FLT3-AML [14]. This is the first and only report on the CER of gilteritinib. In this study, the total incremental cost compared with salvage chemotherapy was $148,106 [14], and the incremental cost per QALY gained was $115,192. This incremental cost was similar to the best supportive care ($107,435). Our results indicated that the incremental CER compared with chemotherapy was $52,270 in gilteritinib and $47,363 in quizartinib. According to the Institute for Clinical and Economic Review [15], these incremental costs are less than $100,000–$150,000; therefore, they are eligible for medical cost policy [15]. Although there is no current research on the outcomes of quizartinib (as of January 1, 2022), our results estimate outcomes to be similar to those of gilteritinib. Since FLT3-AML fulfills the unmet medical needs [4], FLT3 inhibitor monotherapy is recommended for elderly patients with FLT3-AML, such as situationally unfit elderly and relapse and refractory cases post SCT recurrence. Although FLT3 inhibitors have a higher drug cost than conventional chemotherapy, their promising survival benefit can offset the cost.
In conclusion, our study is the first cost-effective cross-sectoral analysis of FLT3 inhibitor in AML compared with TKIs in Ph\(^+\) AL. This study advocates for the clinical application of molecular target therapy in patients unfit for intensive chemotherapy.

3. Limitation

This study is the result of analysis with limited settings, and reanalysis trials under various conditions are desired depending on the purpose. For instances, this study is lacking some analytic methods such as sensitivity analysis or Monte Carlo simulation. And this study did not compensate cost for adverse reaction such as drug side effect. Farther, this study did not include direct non-medical cost (such as transport or food and health care) and indirect (such as cost for social deficit).

In the future, CER would be more superior by optimizing treatment indication and improving therapeutic effect.

4. List Of Abbreviations

cost-effectiveness ratio; CER

chemotherapy; CT

Dasatinib; D

FMS-like tyrosine kinase 3; FLT3

FLT3 mutated acute myeloid leukemia; FLT3-AML

Gilteritinib; G

National Institute for Health and Care Excellence; NICE

Ponatinib; P

Philadelphia chromosome-positive acute leukemia; Ph\(^+\) AL

Quizartinib; Q

stem cell transplantation; SCT

tyrosine kinase inhibitors; TKI

the World Health Organization; WHO
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Statement of Ethics: This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The study protocol was approved by the institute’s committee on human research.

Consent to participate: The written informed consent was waived by the optout procedure and this process was approved by approved the internal review committee of the Kagawa University Hospital.

Consent for publication: Written informed consent was obtained from the patient for publication of this study (including publication of images).

Availability of data and materials: The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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Author Contributions: OI and TI managed the patient’s case, contributed to the literature search, and wrote the manuscript. JIK and MU made substantial contributions to the concept and design of this report. HF qualified the patient’s data, suggested important intellectual content. MU took part in critical discussions. NK was involved in supervision of the manuscript and managed the research. All authors approved the final version of the manuscript.

References


13. Rousselot P, Delannoy A. Optimal pharmacotherapeutic management of acute lymphoblastic leukaemia in the elderly. Drugs Aging. 2011 Sep 1;28(9):749-64. doi: 10.2165/11592850-000000000-


Figures
Figure 1

(a) The CERs for Ph\(^+\) AL treated with SCT / CT / dasatinib (D) / ponatinib (P) were $322,375 / $34,928 / $61,104 / $46,234, respectively.

Figure 1

Cost effectiveness ratio for Philadelphia chromosome-positive acute leukemia and FLT3 mutated AML treated with stem cell transplantation, chemotherapy and molecular target agents.

(a) The CERs for Ph\(^+\) AL treated with SCT / CT / dasatinib (D) / ponatinib (P) were $322,375 / $34,928 / $61,104 / $46,234, respectively.
(b) The CERs for FLT3-AML treated with SCT / CT / gilteritinib (G) / quizartinib (Q) were $355,270 / $42,717 / $94,987 / $90,080, respectively.

*Abbreviations: cost-effectiveness ratio (CER); cytotoxic chemotherapy (CT); FMS-like tyrosine kinase 3 (FLT3); FLT3 mutated acute myeloid leukemia (FLT3-AML); Philadelphia chromosome-positive acute leukemia (Ph+ AL); stem cell transplantation (SCT)