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Complete Cytogenetic Response and Major Molecular Response as Surrogate Outcomes for Overall Survival in First-Line Treatment of Chronic Myelogenous Leukemia: A Case Study for Technology Appraisal on the Basis of Surrogate Outcomes Evidence

Ciani Oriana, MSc[1,*], *Hoyle Martin, PhD*[1], *Pavey Toby, PhD*[2], *Cooper Chris, MA*[1], *Garside Ruth, PhD*[3], *Rudin Claudius, MD*[4], *Taylor Rod, PhD*[1]

[1]*PenTAG, Institute of Health Services Research, University of Exeter Medical School, Exeter, UK;* [2]*School of Human Movement Studies, University of Queensland, Brisbane, Australia;* [3]*European Centre for Environment and Human Health, University of Exeter Medical School, Truro, UK;* [4]*Royal Devon and Exeter NHS Foundation Trust, Exeter, UK*

ABSTRACT

Objectives: In 2012, the National Institute for Health and Care Excellence assessed dasatinib, nilotinib, and standard-dose imatinib as first-line treatment of chronic phase chronic myelogenous leukemia (CML). Licensing of these alternative treatments was based on randomized controlled trials assessing complete cytogenetic response (CCyR) and major molecular response (MMR) at 12 months as primary end points. We use this case study to illustrate the validation of CCyR and MMR as surrogate outcomes for overall survival in CML and how this evidence was used to inform National Institute for Health and Care Excellence's recommendation on the public funding of these first-line treatments for CML. **Methods:** We undertook a systematic review and meta-analysis to quantify the association between CCyR and MMR at 12 months and overall survival in patients with chronic phase CML. We estimated life expectancy by extrapolating long-term survival from the weighted overall survival stratified according to the achievement of CCyR and MMR. **Results:** Five studies provided data on the observational association between CCyR or MMR and overall survival. Based on the pooled association between CCyR and MMR and overall survival, our modeling showed comparable predicted mean duration of survival (21–23 years) following first-line treatment with imatinib, dasatinib, or nilotinib. **Conclusions:** This case study illustrates the consideration of surrogate outcome evidence in health technology assessment. Although it is often recommended that the acceptance of surrogate outcomes be based on randomized controlled trial data demonstrating an association between the treatment effect on both the surrogate outcome and the final outcome, this case study shows that policymakers may be willing to accept a lower level of evidence (i.e., observational association).

Keywords: chronic myeloid leukemia, complete cytogenetic response, dasatinib, health technology assessment, HTA, imatinib, intermediate outcomes, major molecular response, nilotinib, surrogate end points, systematic review, technology appraisal.

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Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm of hematopoietic stem cells [1]. CML used to be regarded as a progressive disease whose natural history evolves through three phases: the initial chronic phase, during which the disease is stable or at the most only slowly progressive, followed after a variable interval by transition through an accelerated phase to a rapidly fatal blast crisis [2–4]. Approximately 90% of the people affected by CML are diagnosed during the chronic phase, with a median age at diagnosis of around 65 years [2]. In the United States, about 4800 to 5200 new cases are diagnosed every year, which corresponds to an annual incidence of 1.0 to 1.3 per 100,000 population [5,6]. Similar annual age-standardized incidence rates have been published for the United Kingdom (i.e., 1.1 per 100,000 for men and 0.7 per 100,000 for women) [7]. Before the introduction of tyrosine kinase inhibitor (TKI) therapy, the median survival time after diagnosis was 6 years [6], with a predicted 5-year overall survival of 42.7% [8] and estimated prevalence of 25,000 to 30,000 cases in the United States [6] and of 4,000 to 5,000 cases in the United Kingdom [9].

The molecular pathogenesis of CML is well understood, and the disease presents the Philadelphia chromosome (Ph) as a molecular hallmark [10]. This fusion gene is the result of a reciprocal chromosomal translocation (i.e., t [9;22]), also known as breakpoint cluster region-Abelson (BCR-ABL) oncogene, that codes for BCR-ABL transcripts and fusion proteins with unusual tyrosine-kinase activity [11,12]. Diagnosis is confirmed by the identification of

* *Address correspondence to:* Ciani Oriana, PenTAG, Institute for Health Services Research, University of Exeter Medical School, Veysey Building, Salmon Pool Lane, EX2 4SG Exeter, UK.

E-mail: oriana.ciani@pcmd.ac.uk.

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either the Ph or the BCR-ABL transcripts, in peripheral blood or bone marrow cells, through cytogenetic [11–14] analysis or reverse transcriptase polymerase chain reaction (PCR), which can be semi-quantitative (real-time PCR or quantitative PCR) [15]. Following recognition of the importance of achieving a certain depth of response at different time points for patients with newly diagnosed CML in chronic phase, the European LeukemiaNet has established guidelines on therapeutic milestones that should be achieved [15]. A complete cytogenetic response (CCyR) is defined as absence of the Ph among at least 20 cells in metaphase in a bone marrow aspirate [16], while a major molecular response (MMR) is reached if the standardized BCR-ABL:ABL ratio is less than 0.1%, which is equivalent to a 3 log reduction from the 100% baseline for untreated patients [17,18].

Knowledge of the molecular basis of this neoplastic disease has led to a new generation of drugs, the TKIs, radically changing the previous standard of care based on interferon-alpha (IFN-α) for patients with CML [13,14]. Imatinib, the first rationally developed selective TKI to be approved for the treatment of a cancer [19] by the European Medicines Agency in 2001, was rapidly adopted as first-line medical treatment for CML in chronic phase in the National Health Service in the United Kingdom [20]. The efficacy of imatinib in comparison with older treatments has been confirmed in a single randomized controlled trial (RCT), the International Randomized Study of Interferon and STI571 (IRIS) trial [14], a prospective, multicenter, open-label, phase 3 RCT comparing imatinib 400 mg/day with IFN-α plus cytarabine. In early 2012, two newer TKIs—dasatinib [17,21] and nilotinib [22–24]—initially promoted for the treatment of patients resistant or intolerant to imatinib [15,25], have been assessed by the National Institute for Health and Care Excellence (NICE) as alternative first-line treatments to imatinib in England and Wales [26]. The evidence of the relative effectiveness of these three alternative treatment options was based on two comparative RCTs, one that compared dasatinib with imatinib [21] (Dasatinib vs. Imatinib in Patients With Newly Diagnosed Chronic Phase CML, the DASISION trial) and the other comparing nilotinib with imatinib [24] (Evaluating Nilotinib Efficacy and Safety in clinical Trials-newly diagnosed patients, the ENESTnd trial). In both trials, the primary end points were biomarkers, that is, confirmed CCyR by 12 months in DASISION and MMR at 12 months in ENESTnd. Although average survival from diagnosis can reach 15 years [25] among this population, these two trials provide only immature data on overall survival with a maximum follow-up of 2 years at the time of the assessment.

Central to this coverage decision, therefore, was consideration of CCyR and MMR as valid surrogate outcomes (i.e., biomarkers intended to substitute and predict for a final patient-relevant outcome [27]) for long-term overall survival in first-line TKI therapy for chronic phase CML to determine estimates of life-years gained across alternative treatments [28].

The dual aims of this study were 1) to assess the evidence base for the use of CCyR and MMR as surrogates for overall survival in patients with chronic phase CML treated with TKI (i.e., dasatinib, nilotinib, and imatinib) and 2) to describe how this evidence was used to predict long-term survival in the related cost-effectiveness model. The policy implications of the validation and use of surrogate outcomes in coverage decisions will be discussed.

Methods

This study consisted of two distinct methodological steps: 2) a systematic review and meta-analysis of the evidence base to quantify the association between CCyR and MMR as surrogates for overall survival in chronic phase patients with CML treated with first-line TKIs and 2) modeling of the observed CCyR and MMR at 12 months to predict long term (>12 months) patient survival in first- and second-generation TKI therapies.

Systematic Review and Meta-Analysis

Our systematic review and meta-analysis was conducted and reported in accord with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [29].

Search strategy

We initially identified studies from a previous systematic review of imatinib for first-line treatment of CML in chronic phase [30]. The following bibliographic databases were searched: Medline, Medline in Process, Embase, PsycINFO (all via OVID), The Cochrane Library, Web of Science (via ISI), and Econlit (via CSA) from October 2002 (the end date of the previous systematic review [30]) to May 2012. The searches were limited to the English language. The Medline search strategy is reported in the Supplemental Material found at http://dx.doi.org/10.1016/j.jval.2013.07.004.

Inclusion criteria

Studies were included if they considered 1) adults (median age > 18 years) with chronic phase CML based on cytogenetic and/or fluorescence in situ hybridization and/or reverse transcriptase polymerase chain reaction results; 2) patients treated with dasatinib, nilotinib, or imatinib; 3) patients naive to previous interferon or TKI treatment; and if they 4) reported the association between CCyR or MMR at 12 months and overall survival. We excluded studies published only as conference abstracts, narrative reviews, editorials, opinion pieces, and individual case studies, or studies whose findings were not judged to be generalizable to the CML population in the United Kingdom or Western countries. Where a study had been reported in several publications, we considered the article with the longest follow-up. Titles, abstracts, and full text of any potentially relevant studies were independently screened by two reviewers (O.C. and T.P.) with any discrepancies resolved by discussion, with the involvement of a third reviewer if necessary.

Data extraction and quality assessment

The methodological quality of included studies was assessed according to a modified list of criteria specified by the National Health Service Centre of Reviews and Dissemination [31]. Study characteristics and data were extracted by one reviewer (O.C.) by using a standardized data extraction form and independently checked by a second reviewer (T.P. or R.T.). To judge the reliability of CCyR and MMR at 12 months as surrogate measures for long-term overall survival, we referred to the following surrogate validation criteria: 1) evidence from RCTs demonstrating treatment effects on the surrogate correspond to treatment effects on the patient-relevant outcome, 2) evidence from observational studies demonstrating consistent association between surrogate outcome and final patient-relevant outcome, and 3) evidence of biological plausibility of relationship between the surrogate outcome and the final patient-relevant outcome [32].

Data analyses

For each study, overall survival was extracted at each year following trial recruitment (or randomization) up to the latest follow-up point reported, separately according to whether a CCyR or an MMR was achieved at 12 months. In all studies, overall survival data were estimated by the Kaplan-Meier method by using landmark analysis to evaluate differences in the final patient-relevant outcomes between responders and nonresponders.

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