The relative efficacy of treatments in first-line management of newly diagnosed chronic myeloid leukaemia: systematic literature review and indirect comparison

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Introduction

• Chronic myeloid leukaemia (CML) is a myeloproliferative disorder of blood stem cells, largely characterised by the presence of an abnormal gene. 1

• Targeted kinase inhibitors (TKIs), including imatinib, dasatinib and nilotinib, are targeted therapies used in the treatment of CML. 2

• The vast majority of TKIs are used as first-line therapies, although some are also used as second-line treatments and, more recently, approved as frontline treatments for CML. 3

• A systematic literature review (SLR) and network meta-analysis (NMA) were conducted in 2011 to compare imatinib, dasatinib and nilotinib as first-line treatments for CML. 4 Dasatinib and nilotinib were second-generation TKIs used as second-line treatments and, more recently, approved as first-line treatments for CML. 5

Methods

Systematic literature review

• A comprehensive SLR was conducted to update a previous SLR conducted in March 2011 6 identifying trials comparing first-line treatments in patients with CML (not previously treated with TKIs).

• Structured searches were conducted on 27 January 2014 in MEDLINE, Embase and the Cochrane Library, date restricted from March 2011 onwards. Hand searching of reference lists, conference abstracts and selected clinical trials registers was also conducted.

Indirect comparisons

• Studies included in the SLR were scrutinised with regard to study design, patient characteristics, interventions and other confounding factors to ensure they were sufficiently homogeneous to allow for a robust meta-analysis.

• Indirect comparisons (ICs) were conducted to compare treatment efficacy using a fixed-effect Bayesian model implemented in WinBUGS software. A fixed-effect model was appropriate due to the small number of studies included.

• Outcomes of interest included complete cytogenetic response (CCyR), major molecular response (MMR) and overall survival (OS) for each treatment arm.

• Relative treatment effects were presented as Odds Ratios (ORs) and 95% Confidence Intervals (CIs) using a network of evidence. Of the 74 publications identified in the SLR, 37 were excluded (see Table 1) or dasatinib (NordCML006

Figure 1: Flow diagram of publications included in updated SLR

Table 1: Included studies and patient characteristics4

Figure 2: Evidence network for CCyR and MMR by various time points

Table 2: Comparison of included trials of interest1,3

Figure 3: CCyR results

Figure 4: MMR results

Conclusions and limitations

• Analyses including all available RCTs support that the second-generation TKIs, dasatinib and nilotinib, are more effective than imatinib from 6 months and that there is no significant difference between dasatinib and nilotinib for the first few time points after initial diagnosis. This is consistent with the findings reported in current guidance for the treatment of CML. 11, 12 and is supported by previous data and real-world evidence.

• The inclusion of nilotinib 800 mg in the evidence network for CCyR and MMR outcomes by specific time points is summarised in Figure 4. The mean odds ratios (ORs) for each treatment by each time point are summarised in Figure 3. Nilotinib was significantly more efficacious than imatinib in terms of achieving CCyR by all time points. Compared with imatinib, dasatinib was significantly more efficacious in terms of achieving CCyR by 6 and 12 months.

• The mean ORs for MMR associated with each treatment by each time point are summarised in Figure 4. Compared with imatinib, dasatinib and nilotinib were significantly more efficacious in terms of achieving MMR by all time points.

• There was no significant difference between dasatinib and nilotinib for MMR by any time point.

References


5. Blood. 2012 16 Nov;120 (21). The mean ORs for MMR associated with each treatment by each time point are summarised in Figure 4. Compared with imatinib, dasatinib and nilotinib were significantly more efficacious in terms of achieving MMR by all time points. There was no significant difference between dasatinib and nilotinib for MMR by any time point.

6. 21 Oct;122 (21).


9. 12. Further analysis is ongoing to present results at various time points. This will consider only patients who had achieved CCyR or MMR and maintained the response at specific time points.