Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia: a systematic review and economic evaluation

Loveman E, Cooper K, Bryant J, Colquitt JL, Frampton GK, Clegg A

CRD summary
This review concluded that, despite data limitations, results of single-arm studies suggested that therapies of high-dose imatinib can lead to improvements in haematological and cytogenetic responses in patients with imatinib-resistant chronic myeloid leukaemia. These conclusions reflect the evidence presented and are likely to be reliable.

Authors’ objectives
To update the evidence on the clinical effectiveness of dasatinib, nilotinib and high-dose imatinib within their licensed indications for the treatment of imatinib-resistant chronic myeloid leukaemia.

This abstract addresses only the clinical effectiveness section of the report as it met the inclusion criteria for DARE. The full report also addresses cost-effectiveness.

Searching
MEDLINE, EMBASE, CINAHL, MEDLINE In-Process & Other Non-Indexed Citations, The Cochrane Library, Science Citation Index Expanded, metaRegister of Controlled Trials, ISRCTN Register, World Health Organisation International Clinical Trials Registry Platform Portal and ClinicalTrials.gov. Reference lists of relevant papers were screened. Conference proceedings from key relevant conferences were searched. Experts in the field were contacted to identify additional relevant studies.

Study selection
Randomised controlled trials (RCTs) and prospective clinical controlled studies that evaluated dasatinib, nilotinib or high-dose imatinib in patients (≥18 years) with imatinib-resistant chronic myeloid leukaemia in the chronic, accelerated or blast-crisis phase were eligible for inclusion. Single-arm prospective cohort studies were eligible where there was no higher level evidence. Studies of high-dose imatinib (>400mg twice daily in chronic phase) as the first-line treatment were excluded. Eligible comparators were dasatinib, nilotinib, high-dose imatinib, hydroxycarbamide, interferon alpha, acute leukaemia-style chemotherapy, allogeneic stem cell transplant, standard-dose imatinib or best supportive care. Eligible studies had to report at least one of the outcomes: treatment response rates (molecular, cytogenetic and haematological responses), time to response, duration of response, overall survival, event-free survival, progression-free survival, time to treatment failure, health-related quality of life and adverse effects.

Most of the included studies only recruited patients with chronic-phase chronic myeloid leukaemia; one study also included very small numbers with accelerated phase and blast crisis. All the single-arm cohort studies had a single high-dose imatinib arm (escalated from 400mg to 600mg or 800mg per day). The included RCT compared high-dose imatinib 400mg twice daily with dasatinib 70mg twice daily. None of the studies reported on concurrent treatment. Failure on standard-dose imatinib was defined in terms of resistance and suboptimal cytogenetic, haematological and molecular response. The definition of imatinib failure slightly varied between included studies. From 45% to 71% of the patients were men. Patient ages ranged from 18 to 85 years. Only the included RCT reported duration of chronic myeloid leukaemia from diagnosis to imatinib therapy (range 14 to 133 months). The RCT was a multicentre trial conducted in 58 centres in 23 countries (including UK, Europe, Russian Federation and Asia). The single-arm cohort studies were conducted in South Korea, Italy and India.

Study selection was performed by one reviewer and checked by a second. Any disagreements were resolved by discussion.

Assessment of study quality
The quality of RCTs was assessed based on 16 criteria including power calculation, randomisation, allocation concealment, baseline comparability, blinding, withdrawals/drop-outs, intention-to-treat analysis and generalisability of the results.
The quality of cohort studies was assessed based on 11 criteria including independent assessment of the main outcome, prospective recruitment, receiving the same intervention for all participants, adequate description of any concurrent therapies, withdrawals/drop-outs and generalisability of the results.

Quality assessment was performed by one reviewer and checked by a second. Any disagreements were resolved by consensus or consultation of a third reviewer.

Data extraction
Data were extracted using a standardised form for all pre-specified outcomes.

Methods of synthesis
The studies were combined in a narrative synthesis with data tables. The included RCT was not treated as a comparative study and only data from the single arm receiving treatment were reported.

Results of the review
Four studies (one RCT, 150 participants and three single-arm cohort studies, 235 participants) included new data published since the PenTAG report (see Other Publications of Related Interest). No new studies of nilotinib were identified. Only new data that were not included in the previous PenTAG report were synthesised in the updated report. This section only reports the results for these new data. The RCT (an open label trial) was judged to be of low quality. All the single-arm cohort studies were judged to be of suboptimal quality.

Benefits and risks of dasatinib (one study): The updated data of the dasatinib arm of the RCT showed that 43.6% of patients had a complete cytogenetic response at the 26-month follow-up, 90% of patients maintained a major cytogenetic response at the 18-month follow-up and 28.7% of patients achieved a major molecular response. An estimated 59% of patients had no treatment failure at the 24-month follow-up.

Adverse events: Seven per cent of patients who received dasatinib had grade 3-4 fluid retention. Reported adverse events associated with dasatinib included fluid retention, bleeding, infection and upper respiratory tract infection and inflammation. Longer follow-up was associated with additional adverse events.

Benefits and risks of high-dose imatinib (four studies): One high-dose imatinib arm of the RCT and three single-arm cohort studies assessed high-dose imatinib. Data from these four cohorts showed that 18% to 36% of patients who received high-dose imatinib achieved a complete cytogenetic response, 33% to 64% achieved a major cytogenetic response and 56% to 82% achieved a complete haematological response. One study reported that around 75% of patients maintained a major cytogenetic response at 18-month follow-up. One study reported that 34% of patients had event-free survival of at least two years. Two studies reported that 65% to 87% of patients had progression-free survival of at least two years. Two studies reported overall survival and 85% to 93% of patients survived at least two years.

Adverse events: Up to 40% of patients had grades 3-4 haematological adverse events. Reported non-haematological events included anorexia, diarrhoea, fatigue, muscle spasms, musculoskeletal pain, superficial oedema and rash; only 5% of patients experienced the grade 3-4 non-haematological adverse events. The discontinuation rate due to adverse events ranged from 0% to 20%.

Cost information
The cost-effectiveness analysis conducted by the authors showed that the three therapies (dasatinib, nilotinib and high-dose imatinib) had similar costs and effectiveness. Due to slightly lower costs and better effectiveness, both nilotinib and dasatinib were slightly more cost-effective than high-dose imatinib. Dasatinib, nilotinib and high-dose imatinib were all cost-effective compared with hydroxycarbamide, with a willingness to pay of about £30,000 per quality-adjusted life year (QALY).

Authors' conclusions
Despite the data limitations, results of single-arm studies suggested that therapies of high-dose imatinib can lead to improvements in haematological and cytogenetic responses in patients with imatinib-resistant chronic myeloid...
leukaemia.

**CRD commentary**
This review addressed a clear research question and was supported by appropriate inclusion criteria. Various relevant databases were searched. Efforts were made to find both published and unpublished studies, which minimised the risk of publication bias. No language restrictions were applied to the searches but the authors stated that they were not able to retrieve some papers in languages other than English due to time and resource constraints. Therefore, some relevant studies may have been missed. Sufficient attempts were made to minimise errors and biases during each stage of the review process. Appropriate criteria were used to assess the quality of included studies and all studies were of low quality.

A narrative synthesis was appropriate due to high levels of clinical heterogeneity across studies in terms of study design, interventions and baseline characteristics of the populations. The synthesis took into account the quality of the evidence.

This review was generally well conducted. The authors’ conclusions acknowledged data limitations and reflected the evidence presented. The conclusions are likely to be reliable.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implication for practice.

**Research:** The authors stated that a three-arm randomised clinical trial of dasatinib, nilotinib and high-dose imatinib was required to assess the relative effectiveness of these therapies in patients with imatinib-resistant chronic myeloid leukaemia.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.