Summary

There are no data available comparing dasatinib with another therapy in this setting. Therefore it is difficult to put the treatment benefit of dasatinib (if there is a benefit) in to context.

The economic model provided by the manufacturer to SMC and AWMSG for their reviews compares dasatinib 70mg twice daily with high dose imatinib (400mg twice daily) in patients with lymphoid blast chronic myeloid leukaemia (LB-CML) and Philadelphia chromosome-positive acute lymphoblastic leukaemia (Ph+ ALL) that are resistant to usual dose imatinib. The use of dasatinib in patients intolerant to usual dose imatinib has not been considered. Due to a lack of data, the model is essentially based on that used for blast phase CML and relies upon a number of assumptions related to disease progression, the utility values associated with response to treatment, and the impact and costs of adverse events. The SMC estimates a cost/QALY of £63,727.

The CDF submission for dasatinib in second line Ph+ ALL was specifically for patients resistant to imatinib. The clinical trials also included a small number of patients intolerant to imatinib.

Final results of the phase II START-L trial are still awaited.

Background

Acute lymphoblastic leukaemia (ALL) is a cancer that affects lymphocytes and lymphocyte-producing cells. Lymphocytes are white blood cells that produce antibodies and are vital for the body's immune system. In ALL there is an excess production of immature lymphocyte-precursor cells called blast cells in the bone marrow. Eventually, the production of normal blood cells is affected by this and there is a reduction in the numbers of red cells, white cells and platelets in the blood.

ALL is the only form of leukaemia that is commonest in childhood (under 15 years of age). ALL occurs more frequently between the ages of 15 to 25 and in those over 75 years compared with other age groups. Estimates for the incidence of ALL in the UK ranges from 200 to approximately 600 per year. In 2003, 253 people died of ALL in England and Wales (1).

Estimates suggest that 20-30% of adults with ALL have a chromosomal abnormality commonly known as the 'Philadelphia chromosome'. This is a reciprocal translocation between parts of the long arms of chromosome 22 and chromosome 9. This results in the fusion of the BCL and ABL genes and the production of a deregulated tyrosine kinase oncoprotein. Prevalence of Philadelphia chromosome positive (Ph+) ALL in adults increases with age and adults with Ph+ ALL have poor prognosis with less than 10% 5-year survival rate (1).

The aim of treatment in ALL is to achieve a cure. First line treatment of newly diagnosed Ph+ ALL is with a variety of combination chemotherapies, most commonly imatinib. Younger
patients with compatible donors are candidates for allogenic bone marrow transplants. Imatinib is also used for consolidation or maintenance therapy. Resistance to imatinib may develop and therapeutic options following resistance to imatinib are limited (1).

The standard approach for second-line treatment of Ph+ ALL is either palliation or attempts at re-induction with combination chemotherapy, such as FLAG-IDA (fludarabine, cytarabine, G-CSF, and idarubicin), or clofarabine/cyclophosphamide. Combination chemotherapy has a poor outcome.

Dasatinib is a second generation tyrosine kinase inhibitor that inhibits both the BCR-ABL kinase and the SRC family kinase, the latter of which is thought to be involved in an alternative signalling pathway in imatinib-resistant ALL. Dasatinib displayed a 325-fold increase in potency in inhibiting \textit{in vitro} growth in cells with wild type \textit{BCR-ABL} compared with imatinib, and maintained activity against cells harbouring imatinib-resistant ABL kinase domain mutations with the exception of T3151, V299L, and F317L mutations (2).

Dasatinib is licensed for the treatment of Ph+ acute lymphoblastic leukaemia (ALL) with resistance or intolerance to prior therapy at a dose of 140mg daily (3).

\textbf{Epidemiology}

Cancer Research UK report that the UK standardised incidence rate for leukaemia in 2008 was 9.6 per 100,000 population (4).

It is reported that 10\% of leukaemia cases are ALL, i.e. 0.96 per 100,000 population (5).

20–30\% of these patients will Ph+, i.e. 0.3 per 100,000 population (1).

It is reported that up to 30\% of these patients are refractory to imatinib and relapse occurs after a median of 2.2 months. Therefore this leaves 0.1 people per 100,000 population who are eligible for dasatinib within this indication (6).

\textbf{Published data}

\textbf{National Guidance}

NICE have published a draft scope on the use of dasatinib for the treatment of Ph+ ALL in adult patients who have resistance to, or are intolerant of, prior therapy. The technology appraisal was suspended and there is no date for when the appraisal is likely to be published (1).

The Scottish Medicines Consortium (SMC) in April 2007 and the All Wales Medicines Strategy Group (AWMSG) in December 2007 both made the decision to not recommend dasatinib for the treatment of adults with Ph+ acute lymphoblastic leukaemia with resistance or intolerance to prior therapy. The decisions were based primarily on cost effectiveness (7) (8).

The AWMSG considered blast phase CML and Ph+ ALL together when making the recommendation.

\textbf{Published trials}

A search of the literature identified a phase III randomised, open-label trial (Lilly M.B. et al, 2010), published interim results of a phase II single arm, open-label study (Ottmann O. et al, 2007), a phase I dose escalation study (Talpaz M. et al, 2006) and some case reports.
Phase III trial

Lilly M.B. et al conducted a randomised, open-label, multi centre phase III trial comparing the efficacy and safety of dasatinib 70mg twice daily with dasatinib 140mg once daily in 609 patients with CML accelerated phase (CML-AP), CML blast phase (CML-BP), or Ph+ ALL who were resistant or intolerant to imatinib (6).

Patients were stratified according to disease type (CML-AP, CML-BP, or Ph+ ALL) and imatinib status (resistance or intolerance). There were 85 patients enrolled with Ph+ ALL in 44 sites worldwide. 40 patients were randomised to dasatinib 140mg once daily and 44 patients to dasatinib 70mg twice daily; one patient was ineligible.

Eligibility criteria included primary or acquired haematological resistance to imatinib, adequate hepatic and renal function, ECOG performance status of 2 or less. Exclusion criteria included prior dasatinib therapy, imatinib therapy within 7 days of initiation, uncontrolled or significant cardiovascular disease, or a history of significant bleeding disorder unrelated to Ph+ ALL.

Patients were considered imatinib-resistant if they had disease progression or lack of response to treatment with imatinib after a minimum of 4 weeks of therapy at a dose of 600mg daily or more (or 400mg to < 600mg/day if intolerant of ≥600mg/day). Patients were considered imatinib-intolerant if they only tolerated doses less than 400mg daily, or had toxicity possibly related to imatinib at a dose of 400mg daily, or less, that led to discontinuation of therapy.

Therapies other than dasatinib were not permitted during the study, with the exception of hydroxyurea for elevated WBC. Colony-stimulating factors and recombinant erythropoietin were permitted at the discretion of the investigator.

The randomisation between the two groups was balanced. The median age was approximately 51 years (range 15–80 years). Approximately 10% of patients had primary imatinib resistance and approximately 20% were intolerant to imatinib.

The primary efficacy endpoint was major haematologic response (MaHR). Secondary endpoints included overall haematologic response (OHR), major cytogenic response (MCyR), time to and duration of MaHR and MCyR, progression-free survival (PFS), overall survival (OS), and safety.

The criteria for major and minor haematological responses were as follows:

<table>
<thead>
<tr>
<th>Haematologic response criteria</th>
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<tr>
<td><strong>Major haematologic response</strong></td>
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<tr>
<td>a) Complete hematologic response</td>
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<tr>
<td>1) WBC count ≤institutional ULN*</td>
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<tr>
<td>2) ANC ≥1000/mm³</td>
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<tr>
<td>3) Platelets ≥100 000/mm³</td>
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<td>4) No blasts or promyelocytes in peripheral blood</td>
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<td>5) Bone marrow blasts ≤5%</td>
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<td>6) &lt;5% myelocytes plus metamyelocytes in peripheral blood</td>
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<td>7) Basophils in peripheral blood &lt;20%†</td>
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<tr>
<td>8) No extramedullary involvement (including no hepatomegaly or splenomegaly)</td>
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<tr>
<td>b) No evidence of leukaemia</td>
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<tr>
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<tr>
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</tbody>
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| 6) Basophils in peripheral blood <20%† and at least one of the following:
(i) 20 000/mm³ ≤ platelets <100 000/mm³  
(ii) 500/mm³ < ANC <1000/mm³  

**Minor haematologic response**  
a) <15% blasts in bone marrow and in peripheral blood  
b) <30% blasts plus promyelocytes in bone marrow and <30% blasts plus promyelocytes in peripheral blood  
c) <20% basophils in peripheral blood  
d) No extramedullary involvement other than spleen and liver  

WBC indicates white blood cell; ULN, upper limit of normal; and ANC, absolute neutrophil count.  
*ULNs were as follows: 1 centre 8.0, 1 centre 8.8, 1 centre 9.0, 6 centres 10.0, 2 centres 10.8, 6 centres 11.0, 1 centre 11.1.  
†As specified in the study protocol  

An OHR was defined as complete haematologic response (CHR), no evidence of leukaemia (NEL), or minor haematologic response (MiHR). A haematologic response was confirmed if all criteria were met consistently for at least 28 days.  

Cytogenetic responses (CyR) were defined as follows:  
Complete CyR (CCyR) = 0% Ph+ metaphases  
Partial CyR (PCyR) = 0–35% Ph+ metaphases  
Minor CyR = 35–65% Ph+ metaphases  
Minimal CyR = 65–95% Ph+ metaphases  
No CyR = 95–100% Ph+ metaphases  
A minimum of 20 metaphase cells was required. A major CyR (MCyR) was defined as either a CCyR or PCyR.  

After a period of 2 years follow-up the main results were as follows:  
- Two patients in the once-daily group and three patients in the twice-daily group were still on treatment after 2 years  
- The rate of confirmed MaHR (primary efficacy endpoint) in the once-daily group (38%) was not significantly different than that in the twice-daily group (32%) (P=0.650).  
- The rates of confirmed CHR and OHR were similar between once-daily (33% and 48%, respectively) and twice-daily (25% and 41%, respectively) groups.  
- A MCyR was more frequent (70%) in the once-daily group than in the twice-daily group (52%) (P=0.120), as was a CCyR (50% vs. 39%).  
- The median duration of MaHR in responders was 4.6 months in the once-daily group and 11.5 months in the twice-daily group (the author’s state that this difference is likely to be due to the variability resulting from a small number of patients at risk in the later time points of the trial).  
- The median duration of MCyR for the once-daily group (4.1 months) was similar to that for the twice-daily group (4.4 months).  
- The median duration of CCyR for the once-daily group (4.3 months; 95% CI 3.7–6.9) was similar to that for the twice-daily group (5.5 months; 95% CI 3.3–13.4). Of patients with CCyR, 16 out of 20 in the once-daily and 12 out of 17 in the twice-daily group progressed.  
- The median PFS in the once-daily group (4.0 months) was not significantly different from the in the twice-daily group (3.1 months) (P=0.735).  
- The median OS in the once-daily group (6.5 months) was less than that in the twice-daily group (9.1 months) but the difference was not statistically significant (P=0.336).
Ottmann O. et al conducted a single-arm, open-label, multi centre phase II trial (START-L) and interim results, with a minimum follow-up period of 8 months, have been published (9). The study was open to patients over 18 years with Ph+ (or BCR-ABL positive) imatinib-resistant or –intolerant ALL previously treated with standard induction or consolidation chemotherapy, or imatinib-resistant or –intolerant blast cell CML. Patients reported are those treated with Ph+ ALL only. Eligibility criteria and definitions for imatinib-resistant and imatinib-intolerant are as described for the phase III trial above.

The primary objectives were to establish the rates of MaHR and OHR to dasatinib in patients with imatinib-resistant Ph+ ALL. Secondary objectives included rates of MaHR and OHR in patients with imatinib-intolerant disease, duration of all haematologic responses, CyR rates, and the safety and tolerability of dasatinib.

 Eligibility criteria and definitions for imatinib-resistant and imatinib-intolerant are as described above. The median age was 46 years (range 15–85 years). Patients had a median 20-month duration of leukaemia before starting dasatinib (range 3–97 months). Dasatinib was administered at a dose of 70mg twice daily and during the study treatment other than dasatinib for Ph+ ALL was not permitted (with the exception of anagrelide for elevated platelet counts and hydroxyurea for elevated WBC). Erythropoietin and colony-stimulating factors were administered at the investigator’s discretion. Intrathecal chemotherapy was permitted for three patients with evidence of CNS involvement. Haematologic responses had to be maintained for 4 or more weeks with no anagrelide or hydroxyurea used during the same period.

36 patients with Ph+ ALL were enrolled in this study; 34 patients (94%) with imatinib-resistant disease and 2 patients (6%) with imatinib-intolerant disease. Fifteen patients (42%) had undergone prior stem cell transplant, 32 patients (89%) had received chemotherapy, and 3 (8%) had received interferon alpha. 25 patients of those tested (78%) had a BCR-ABL kinase domain mutation at baseline. With a minimum of 8 months follow-up, 9 patients (25%) remained on study. Primary reasons for discontinuation were disease progression (17 patients, 47%) and death (4 patients, 11%). The median duration of therapy was 3.2 months (range 0.2–11.0 months) for the total population, and 8.3 months (range 6.3–11.0) for patients remaining on study.

The main results were as follows:

- The OHR rate was 50% (18/36 patients).
- Major haematologic responses were seen in 42% (15/36) of these patients and the median time to MaHR was 1.8 months.
- The median duration of MaHR had not been reached, and among patients who achieved MaHR, response duration ranged from 1.9 to over 8.7 months. Ten of the 15 patients (67%) who achieved a MaHR had not progressed at the 8-month follow-up.
- Major cytogenetic responses were seen in 58% (21/36) of patients. The authors report that with prior imatinib the MCyR rate was 50% but this statement is not referenced or documented elsewhere in the study.
- Treatment was discontinued for 39% (14/36) of patients before the first on-study cytogenetic assessment, i.e. within the first month of therapy.
- The median PFS was 3.3 months.

Safety

Phase III trial (Lilly M.B. et al, 2010)

Drug-related adverse events occurring in at least 10% of patients were generally similar between the once-daily regimen and twice-daily regimen. The incidences of grade 3–4
neutropenia (once-daily 67% vs. twice-daily 72%) or thrombocytopenia (once-daily 72% vs. twice-daily 60%) were similar between the two groups. Non-haemotologic adverse events were mostly grade 1 or 2 for both dosing schedules with GI events (e.g. diarrhoea, nausea, and vomiting) being the most common. Fewer patients experienced a pleural effusion when dasatinib was administered once daily (all grades 18%; grade 3–4 5%) versus twice-daily (all grades 32%; grade 3–4 14%). The incidence of other fluid-related events was also lower in the once-daily (3%) versus twice-daily (16%) group. Neither of these differences was statistically significant. Fewer patients in the once-daily group compared with the twice-daily group required dose reductions (n=4, 10% vs. n=10, 23%) with nearly all reductions being due to non-haematologic toxicities.

Phase II trial (Ottmann O. et al, 2007)

The most frequent events, irrespective of grade, were gastrointestinal disorders (diarrhoea, nausea), and pyrexia. Severe febrile neutropenia was documented for 4 patients (11%) but this was manageable with dasatinib dose interruptions or reductions and/or medical intervention. Two patients (6%) discontinued treatment due to toxicity. Pleural effusion occurred in 7 patients (19%) with one patient (3%) having grade 3–4. Peripheral oedema was seen in 6 patients (17%) and no patients had grade 3–4 severity.

Cost

The cost of 30 dasatinib 140mg tablets is £3005 (BNF63, March 2012). This price includes VAT at 20%. This is the cost of one month’s treatment for one patient.

The median PFS from the trials above was approximately 4 months. Therefore the cost of treating one patient for 4 months would be £12,000

Using the epidemiology figure of 0.1 per 100,000, the cost per 100,000 population of using dasatinib for this indication would be £1200.

No formal economic analysis was provided to SMC for patients with Ph+ALL treated with dasatinib as a second line therapy. The manufacturer assumed that Ph+ALL patients were similar to blast phase CML patients and estimated a cost/QALY of £63,727.

References

3) Sprycel® (dasatinib) SPC. DOR 21.2.12
6) Lilly M.B et al. Dasatinib 140mg once daily versus 70mg twice daily in patients with Ph-positive acute lymphoblastic leukaemia who failed imatinib: Results from a phase 3 study. American Journal of Hematology. 2010; 85: 164–170


Details of search strategy:

1. EMBASE; DASATINIB/; 4273 results.
2. EMBASE; ACUTE LYMPHOBLASTIC LEUKEMIA/ [Limit to: Human]; 21107 results.
3. EMBASE; 1 AND 2 [Limit to: Human]; 463 results.
4. EMBASE; *DASATINIB/; 935 results.
5. EMBASE; 2 AND 4 [Limit to: Human]; 103 results.
6. MEDLINE; dasatinib.ti,ab; 1054 results.
7. MEDLINE; PRECURSOR CELL LYMPHOBLASTIC LEUKEMIA-LYMPHOMA/ [Limit to: Humans]; 17563 results.
8. MEDLINE; 6 AND 7 [Limit to: Humans]; 90 results.