

New and Emerging Technology Briefing

*National
Horizon
Scanning
Centre*

**Imatinib (Glivec) for
Philadelphia positive
acute lymphoblastic
leukaemia**

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Horizon Scanning Review

Early assessments of new or emerging technologies
contain time-limited information and should be
used with due caution.

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Imatinib (Glivec) for Philadelphia positive acute lymphoblastic leukaemia

Summary

Imatinib (Glivec) is an oral inhibitor of the Bcr-Abl tyrosine kinase that is in phase III trials for patients in all stages of Philadelphia positive acute lymphoblastic leukaemia (Ph⁺ALL). Phase II trials have evaluated imatinib monotherapy and combination therapy, before and after stem cell transplantation, in newly diagnosed, relapsed or refractory disease. The only comparative trial evaluating imatinib against multiagent chemotherapy reported increased complete responses with imatinib (92% versus 53%).

Developer – Novartis Pharmaceuticals Ltd.

Regulatory status – Phase III trials are ongoing.

Unit cost – Imatinib costs about £2,336 per month and £28,032 per annum.

NHS or Government priority - Cancer is a government and NHS priority.

Relevant existing UK guidance – NICE service guideline: Improving Outcomes in Haematology Cancers 2003. NICE guidance: Imatinib for chronic myeloid leukaemia 2003. NICE guidance: Imatinib for gastro-intestinal stromal tumours 2004.

Burden of disease – There were 595 new cases of ALL in England and Wales in 2000. There were 284 deaths from ALL in England and Wales in 2002. ALL accounts for a quarter of all childhood malignancies with 370 new cases each year. Ph⁺ALL occurs in 3-5% of children and 20-30% of adults (an estimated total Ph⁺ALL in 86 patients). The prevalence of Ph⁺ALL in adults increases with age. Adults with Ph⁺ALL have poor prognosis with less than 10% 5-year survival rates. In children 5-year survival rates are between 25-30%.

Potential clinical benefit – The transplant related mortality and disease free survival of the following allogeneic stem cell transplant (alloSCT) is affected by the disease status at the time of transplantation. If imatinib reduces disease activity before alloSCT it may contribute to reducing mortality. The use of imatinib to induce remission or response in those with refractory disease may impact beneficially on morbidity.

NHS or societal resource impact - It is difficult to predict the potential impact of imatinib for Ph⁺ALL until results from the ongoing trials are published. However, if all the estimated 86 patients with Ph⁺ALL receive imatinib 600 mg a day for one year it will cost in the region of £2.4M. It is unclear at present how long a course of treatment will be, in some cases it may be used just prior to stem cell transplantation, so costs will be less. As imatinib is already licensed for chronic myeloid leukaemia there should be no additional organisational impact on haematology services.

Background

Acute lymphoblastic leukaemia (ALL) is a haematological malignancy characterised by the replication of immature lymphocytes which destroy and replace normal cells in the bone marrow. Philadelphia positive acute lymphoblastic leukaemia (Ph⁺ALL) has a poor prognosis and is caused by the formation of the Bcr-Abl fusion protein due to reciprocal translocation between the long arms of chromosomes 9 and 22. The Bcr-Abl proteins display active tyrosine kinase activity which cause the expression of leukemogenesis^{1,2}.

The technology

Imatinib (Glivec) – Novartis Pharmaceuticals Ltd., is an oral selective inhibitor of the Bcr-Abl tyrosine kinase that is in phase III trials for patients in all stages of Ph⁺ALL. It functionally inactivates Bcr-abl by binding competitively to the ATP binding site of the p210 and p190 Bcr-Abl protein kinases^{3,4}. Imatinib will be given orally at 600mg per day.

Imatinib is licensed for newly diagnosed chronic myeloid leukaemia where bone marrow transplantation is not considered first-line treatment, chronic myeloid leukaemia in accelerated phase, chronic phase after failure of interferon- α or in blast crisis, and gastro-intestinal stromal tumours. Imatinib is also in phase II trials for fibroma, prostate cancer, salivary gland cancer, small cell lung cancer, brain cancer, breast cancer, pulmonary fibrosis and acute myelogenous leukaemia.

Burden of disease and patient group

There were 595 new cases of ALL in England and Wales in 2000. There were 284 deaths from ALL in England and Wales in 2002^{5,6}. ALL is the most common childhood cancer and accounts for a quarter of all childhood malignancies with 370 new cases each year⁷. Ph⁺ALL is the most common abnormality associated with ALL and occurs in 3-5% of children and 20-30% of adults with this condition (an estimated total Ph⁺ALL in 86 patients). The prevalence of Ph⁺ALL in adults increases with age. Adults with Ph⁺ALL have poor prognosis with less than 10% 5-year survival rates. In children 5-year survival rates are between 25-30%^{1,4}.

Current treatment and alternatives

In newly diagnosed patients first-line treatment is induction chemotherapy to destroy leukaemia cells. Response rates are between 50-80%. There is a high rate of relapse with subsequent poor prognosis. Survival rates for patients who relapse after primary chemotherapy or are refractory to chemotherapy are between 0-16%^{2,8}.

Allogeneic stem cell transplantation (AlloSCT) is currently the only form of curative treatment. Expert opinion states it has the capacity to induce disease free survival in 30-40% of patients. There are reduced survival rates in patients transplanted in their 2nd or 3rd remissions with long term survival of 17% in 2nd remission and 5% in 3rd remission after 2 years from transplantation^{2,8}. Survival rates after transplant are affected by the disease status at the time of transplantation.

Cost

Imatinib costs about £2,336 per month and £28,032 per year.

Current research evidence**Effectiveness**

An open-label, non-randomised, phase II trial studied the clinical efficacy and safety of imatinib in 56 patients with relapsed or refractory Ph⁺ALL (n=48) or chronic myelogenous leukaemia in lymphoid blast crisis (n=8)². Patients were given 400 mg or 600 mg of imatinib once daily for 24 weeks. Imatinib was continued indefinitely if judged to be beneficial. The primary efficacy endpoint was the rate of sustained haematologic response lasting at least 4 weeks, assessed as complete haematologic response (CHR), complete marrow response (marrow CR), and partial response (PR). Secondary efficacy endpoints were the induction of cytogenetic response, time to disease progression (TTP) and overall survival. The rates of CHR and marrow CR were 19% in patients with relapsed ALL and 10% in refractory ALL. These were sustained for at least 4 weeks in only 6% of the patients. At 6 months patients had an estimated progression free rate of 12%. Median estimated TTP was 2.2 months. Overall survival was 4.9 months.

Interim results from an ongoing randomised, multi-centre, phase II trial comparing imatinib with chemotherapy in patients over the age of 55 with newly diagnosed Ph+ALL have been published in abstract⁹. Patients were randomised to receive a 4-week course of imatinib at 600mg/day or multiagent induction chemotherapy. The abstract reports that 92% of patients receiving imatinib achieved CR and 8% PR, compared to 53% and 7% of those receiving multiagent chemotherapy. Of the 6 patients who have failed multiagent chemotherapy, 4 were transferred to the imatinib group and 3 have achieved CR. The date for final analysis is unknown.

Interim results of an ongoing, phase II trial investigating the use of imatinib in 27 patients with minimal residual disease (MRD) following stem cell transplantation (SCT) have reported in abstract¹⁰. Outcomes included MRD-negativity and median TTP. Results reported that 14 patients achieved MRD-negativity within a median of 1.5 months. Of this group only 2 had relapsed at the 15.6 month follow-up both after imatinib discontinuation. In the 13 patients who did not achieve MRD-negativity 12 relapsed. Median TTP in the MRD negative group was 28.6 months compared to 3 months in the MRD group (p<0.0001).

The prognostic response of pre-treatment disease features and early bone marrow response has been investigated in a study of 68 patients with relapsed or refractory Ph⁺ALL or MRD enrolled in 2 phase II trials of imatinib salvage therapy¹¹. Stem cell transplantation had been performed in 29% (allogenic) and 6% (autologous) of the patients. Patients received 600mg, 400mg or 300mg of imatinib. Overall haematologic response rate was 70%, with 30% in CHR, 29% in marrow CR and 11% in partial remission. 30% were refractory to imatinib. Patients with bone marrow (BM) blasts below 5% on day 14 had CHR or marrow response of 92% and TTP of 5.2 months (p<0.0001). 62.5% of patients with more than 5% BM blasts were non-responders at day fourteen and had a TTP of 0.9 months (P<0.0001). At 6 months progression free survival was 23% (95%CI 17% to 29%). Overall survival was 33.3% (95%CI 27.5% to 39%) at 12 months and 22.6% (95%CI 17.2% to 28%) at 18 months. Discontinuation of imatinib occurred in 78% of patients due to disease progression, 15% due

to allogenic SCT and 1% due to patient decision. Adverse effects due to imatinib included muscle cramps, nausea and fluid retention.

The efficacy and tolerability of imatinib 600mg per day prior to allogenic SCT, has been investigated in a study of 46 patients with relapsed or refractory Ph⁺ALL enrolled in phase II studies of imatinib⁸. Imatinib was continued until disease progression unless there were serious adverse effects. Outcomes were CHR, marrow CR and TTP. 22 patients underwent SCT and received imatinib for a median of 67 days prior to transplantation. 73% achieved CHR or marrow CR within 4 weeks, 9% achieved partial response and 18% were refractory. At the time of SCT 10 patients were in CHR or marrow CR, and 12 had relapsed or were refractory. After SCT 32% relapsed a median of 5.2 months after SCT and 32% were in ongoing remission at a median of 9.4 months. Disease free survival of patients transplanted during complete response was 51% (95% CI 33% to 69%) at 12 months. Disease free survival in those with refractory or relapsing disease was 8% at 7 months.

The effectiveness of combining imatinib with HyperCVAD^a, a dose-intensive chemotherapy regimen, has been studied in 20 patients with Ph⁺ALL who were newly diagnosed with de novo disease (55%), refractory to standard induction chemotherapy (20%) and complete remission (25%) after one course of induction therapy¹. Patients received 400mg daily of imatinib for two weeks of each chemotherapy course. HyperCVAD was alternated with high dose methotrexate and cytarabine (ara-C). Chemotherapy was followed by 13 months of maintenance therapy that included 600mg imatinib daily. Response was measured as complete remission (CR), induction death and resistant disease. All 15 patients who entered the study with active disease achieved CR. 10 patients underwent SCT within a median of 3.5 months in the first CR. Of the remaining 10 patients 1 patient relapsed after one year, 5 remained in CR for a median of 20 months and 2 remained in CR at 15 and 16 months but died due to co-morbid conditions.

The efficacy of combining imatinib with interferon alpha has been investigated in 6 patients enrolled in phase II trials with Ph⁺ALL who were ineligible for stem cell transplantation⁴. Five patients were in CR with minimal residual disease and one was refractory to imatinib. Results showed that of the five patients with MRD 4 remained in CR after a median of 20 months treatment. The refractory patient achieved a marrow CR of 5 months duration. Results show that combination therapy may prolong haematologic and molecular remissions in Ph⁺ALL patients who have not undergone SCT.

Ongoing or related research

An open label, non-randomised study (UKALL XII) of imatinib in patients between the ages of 15-55 years with Ph⁺ALL who have not been previously treated, is ongoing. Patients will receive 600mg/day of imatinib for 4 weeks followed by bone marrow transplant and imatinib therapy indefinitely until relapse of disease. Outcomes include five-year event free survival, and overall rate of cytogenetic response and molecular response. The anticipated end date of the trial is in 2005.

^a HyperCVAD - cyclophosphamide (CY) administered with doxorubicin (DOX), vincristine (VCR), and dexamethasone – often alternated with high-dose methotrexate (MTX) and cytarabine (Ara-C)

A multi-centre, open label trial of imatinib in combination with chemotherapy as part of induction regimen and consolidation therapy in patients with newly diagnosed Ph⁺ALL is ongoing. Outcomes include response rates, failure free survival and overall survival rates.

An open-label, randomised, phase II/III study comparing imatinib in combination with chemotherapy and chemotherapy alone, in children under the age of 17 with Ph⁺ALL is ongoing. The primary endpoint is disease free survival at 4 years. Final analysis is expected in 2012.

Cost impact and projected diffusion

It is difficult to predict the potential impact of imatinib for Ph⁺ALL until results from the ongoing trials are published. However, if all the estimated 86 patients with Ph⁺ALL receive imatinib 600 mg a day for one year it will cost in the region of £2.4M. It is unclear at present how long a course of treatment will be, in some cases it may be used just prior to stem cell transplantation, so costs will be less. As imatinib is already licensed for chronic myeloid leukaemia there should be no additional organisational impact on haematology services.

References

- ¹ Thomas DA, Faderl S, Cortes J, O'Brien S et al. Treatment of Philadelphia chromosome-positive acute lymphocytic leukaemia with hyper-CVAD and imatinib mesylate. *Blood* 2004;103;(12):4396-4407.
- ² Ottmann OG, Druker BJ, Sawyers CL, Goldman JM et al. A phase 2 study of imatinib in patients with relapsed or refractory Philadelphia chromosome-positive acute lymphoid leukemias. *Blood* 2002;100;(6):1965-1971.
- ³ Ottmann OG, Wassmann B, Hoelzer D. Imatinib for relapsed BCR/ABL Positive leukemias. *Ann Hematol.* 2002;81 Suppl 2:S36-7.
- ⁴ Wassmann B, Scheuring U, Pfeider H et al. Efficacy and safety of imatinib mesylate (Glivec[®]) in combination with interferon- α (IFN- α) in Philadelphia chromosome-positive acute lymphoblastic leukaemia (Ph⁺ALL). *Leukemia* 2003;17:1919-1924.
- ⁵ Cancer Research UK, Incidence-UK, Cancer stats, February 2004.
- ⁶ Cancer Research UK, Mortality-UK, Cancer Stats, February 2004
- ⁷ Cancer Research UK, Leukaemia-UK, Cancer Stats, December 2003.
- ⁸ Wassmann B, Pfeifer H, Scheuring U, Klein SA et al. Therapy with imatinib mesylate (Glivec) preceding allogeneic stem cell transplantation (SCT) in relapsed or refractory Philadelphia-positive acute lymphoblastic leukaemia (Ph⁺ALL). *Leukemia* 2002;16:2358-2365
- ⁹ Ottmann OG, Wolfgang JW et al. A randomised phase II study comparing imatinib with chemotherapy as induction therapy in elderly patients with newly diagnosed Philadelphia-positive acute lymphoid leukemias (PHALL). *The Hematology Journal* 2004;5; suppl.2.
- ¹⁰ Wassmann B, Pfeifer H, Bruck P et al. Imatinib induces sustained molecular remissions in post-transplant molecular relapse of PH⁺ acute lymphoblastic leukaemia (Ph⁺ALL). *The Hematology Journal* 2004;5 supp 2:S211.
- ¹¹ Wassmann B, Pfeifer H, Scheuring UJ, Binckebanck A et al. Early prediction of response in patients with relapsed or refractory Philadelphia chromosome-positive acute lymphoblastic leukaemia (Ph⁺ALL) treated with imatinib. *Blood* 2004;103;(4):1495-1498.

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The National Horizon Scanning Centre,
Department of Public Health and Epidemiology
University of Birmingham, Edgbaston, Birmingham, B15 2TT, England
Tel: +44 (0)121 414 7831 Fax +44 (0)121 414 2269
www.pcpoh.bham.ac.uk/publichealth/horizon