

**REGIONAL DRUG AND THERAPEUTICS CENTRE
(NEWCASTLE)**

**THE USE OF DASATINIB
IN THE MANAGEMENT OF
ACUTE LYMPHOBLASTIC LEUKAEMIA
IN ADULTS**

**Wolfson Unit
Claremont Place
Newcastle upon Tyne
NE2 4HH**

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ABOUT THIS REPORT

This is one of a series of evaluations prepared by the Regional Drug and Therapeutics Centre (Newcastle). The aim is to give objective information and guidance to commissioners of health services, prescribers and others both on clinical aspects of the subject and on arrangements for prescribing. The reports are prepared by a multidisciplinary team within the Centre and reviewed by health authority personnel and appropriate external specialists. However, responsibility for the content and conclusions rest solely with the Regional Drug and Therapeutics Centre. We welcome comments on reports and suggestions for future topics. The following reports are available:

<i>Subject</i>	<i>Date issued</i>
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The use of entecavir in the management of chronic hepatitis B infection	March 2007
The use of natalizumab in the management of multiple sclerosis	March 2007
The use of aromatase inhibitors in the treatment of early stage breast cancer (N)	March 2007
Palonosetron for the prevention of nausea and vomiting associated with cancer chemotherapy	March 2007
Alemtuzumab in the management of chronic lymphocytic leukaemia	March 2007
Omalizumab in the management of severe, persistent, allergic asthma	June 2006
Bortezomib second-line in the management of multiple myeloma	March 2006
Adjuvant docetaxel or paclitaxel in the management of early stage breast cancer (N)	March 2006
Erlotinib in the management of non-small cell lung cancer	March 2006
Ibritumomab in the management of B-cell follicular non-Hodgkin's lymphoma	March 2006
Rituximab in combination with CVP chemotherapy for the management of follicular non-hodgkins lymphoma.	March 2006
Pemetrexed in the management of malignant pleural mesothelioma	February 2006
Pegvisomant in the management of acromegaly	January 2006
Ibandronic acid in the management of hypercalcaemia of malignancy, bone pain and the prevention of skeletal events associated with skeletal metastases	August 2005
Teriparatide in the management of osteoporosis	July 2004
Adefovir dipivoxil for the treatment of chronic hepatitis B infection (N)	May 2004
An update on newer agents for the treatment of pulmonary hypertension	February 2004

Older reports are available via our website or on request

Agents which have been reviewed by the National Institute for Health and Clinical Excellence (NICE) are indicated by **(N)** after the report name. Please refer to the NICE website to access their guidance for these agents/conditions.

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SUMMARY

- Acute lymphoblastic leukaemia (ALL) is a disease of proliferation of immature and non-functioning leukocytes. ALL is uncommon in adults, representing about 15% of adult leukaemias resulting in about 800 new cases of adult (≥ 15 years) ALL in England in 2004. Treatment consists of an induction course, followed by two or more consolidation periods, and treatment directed at the central nervous system, followed by long-term maintenance for up to three years. A variety of oral and parenteral cytotoxic and other drugs are used in treatment regimens. The Philadelphia chromosomal abnormality is present in 20% to 30% of cases of adult ALL, and results in a fusion gene that affects cell signalling, proliferation and survival. Patients with this abnormality are described as Philadelphia chromosome-positive (Ph+) and have a poorer prognosis compared with patients without the abnormality.
- Dasatinib is an oral tyrosine kinase inhibitor which binds to active and inactive forms of BCR-ABL kinase resulting from the Philadelphia chromosome. It is licensed for the treatment of adults with chronic, accelerated or blast-phase chronic myeloid leukaemia (CML) with resistance or intolerance to prior therapy, including imatinib, and the treatment of adults with Ph+ ALL and lymphoid blast CML with resistance or intolerance to prior therapy.
- In the treatment of adult Ph+ ALL dasatinib has been evaluated in a small number of patients from larger trial populations. The benefits of treatment with dasatinib were limited for the majority with patients, with treatment ceasing after a median of just 3.2 months and progression-free survival lasting a median of about 3.5 months.
- Patients with Ph+ ALL have high levels of existing morbidity relating to the condition. Dasatinib resulted in a significant but predictable and manageable range of haematopoietic adverse effects, as well as several gastro-intestinal effects such as nausea, vomiting, and diarrhoea. Fluid retention with resultant oedema and effusions was also observed.
- Dasatinib offers an additional treatment option for a group of patients for whom the alternative is supportive care only, although it has not yet been compared to best supportive care in a phase III randomised controlled trial. The actual benefits observed with dasatinib in this patient group are however small and it is unlikely to meet the requirements for cost-effectiveness.
- Dasatinib at the standard maintenance dose of 70 mg twice daily costs about £2,500 per month per patient. The cost for 14 weeks treatment, the median treatment duration observed in one of the larger studies, is £8,515 per patient. The cost per quality adjusted life year gained for dasatinib in patients with Ph+ ALL has been estimated at £64,000 per patient.
- Several other kinase inhibitors are in development with distinct differences in cellular targets and patterns of resistance.

BACKGROUND

Acute lymphoblastic leukaemia (ALL) is a disease causing proliferation of immature and non-functioning leukocytes, specifically lymphoid blast cells.¹ The cause of ALL is not known and several inherited, environmental, and infectious factors have been proposed.^{1,2}

In the course of the disease there is a proliferation and accumulation of leukaemic cells resulting in suppression of normal haematopoiesis and involving various extramedullary sites, specifically the liver, spleen, lymph nodes, thymus, meninges and gonads. The disease can occur in any age group but is most common in children. Therapeutic advances have resulted in a cure rate for childhood ALL in excess of 80% but the survival rate for adult ALL remains less than 40% despite the use of stem cell transplants in many patients. Treatment outcome is particularly poor among patients who relapse on current front-line ALL regimens.³

INCIDENCE AND SURVIVAL

Acute leukaemia is a rare disease with an incidence of about four per 100,000 of the population. The acute leukaemias consisting of ALL and acute myeloid leukaemia comprise over half of all leukaemic disease seen in clinical practice, with ALL accounting for about 25%.²

ALL is predominantly a disease of childhood and is the most common childhood cancer, accounting for 85% of childhood leukaemias. Its incidence is highest in the three- to four-year-old age group, falling off by the age of 10 years with a secondary rise after the age of 40 years.²

ALL is uncommon in adults, representing about 15% of adult leukaemias⁴ resulting in about 800 new cases of adult (≥ 15 years) ALL in England in 2004.⁵ The estimated incidence of adult ALL is about 1.6 per 100,000 of the population.⁶

Adult ALL is potentially curable with leukaemia-free survival rates of 35% to 45% achievable.² The European relative survival rate at five years post-diagnosis for the period 1990-94 for adult patients with ALL was 24% (25% for men and 23% for women). The rate decreased markedly with patient age from 37% to 3% from the youngest age group (15 to 45 years) to the oldest (≥ 75 years).⁴

SYMPTOMS

The clinical features of acute leukaemia are related to bone marrow failure and the effects of organ infiltration. The former can result in anaemia and attendant symptoms (weakness, lethargy, pallor); neutropenia and resultant increased incidence of infection causing fever and malaise; and thrombocytopenia resulting in spontaneous bruising, purpura, bleeding gums, and nose bleeds. Infiltration of malignant cells into the central nervous system (CNS) can cause headaches, nausea, vomiting, blurred vision and diplopia. Infiltration into the bones can cause tenderness and pain. There may also be superficial lymphadenopathy and, more rarely, testicular swelling or mediastinal compression.²

DIAGNOSIS

Diagnostic tests include a full blood screen, bone marrow aspiration, chest X-ray, lumbar puncture for cerebrospinal fluid (CSF) screening, and immunophenotyping. Typically the signs observed will be a normocytic and normochromic anaemia, an abnormal differential white blood cell count (WBC), and thrombocytopenia.²

A diagnosis of ALL is established when a bone marrow examination reveals a lymphoid blast cell content in excess of 20% of total cellularity.⁴

CLASSIFICATION AND PROGNOSIS

ALL is classified into different cell lineages based on surface antigen expression.

- Common ALL: possessing the common ALL antigen (c-ALL)
- T-cell type: T-ALL
- B-cell type: B-ALL
- Null: non-B, non-T, and lacking c-ALL

The subtypes display different clinical presentations, responses to treatment, and ultimately prognoses, with c-ALL having the best prognosis and B-ALL the worst.²

ALL is a heterogeneous disease consisting of various specific immunological subtypes. It is important that the type of ALL is identified as it has prognostic significance and will dictate treatment options. In adult patients approximately 20% of cases of ALL are T cell in origin, 75% are early (precursor) B cell, and 5% are more mature B cell-derived.¹

Certain groups of patients carry a less favourable prognosis: those with a high WBC count, male gender, B-ALL, Philadelphia chromosome-positive and other translocations, more than four weeks to first remission, and CNS disease at presentation.²

Numerous cytogenetic variations may be present in ALL with some conferring specific drug resistance or susceptibility and others having important prognostic value.^{7,8} One of the most important is the Philadelphia chromosome, a reciprocal translocation between chromosome 22 and chromosome 9. Patients who possess this abnormality are said to be Philadelphia chromosome-positive (Ph+). It has important prognostic value in ALL with Ph+ patients having reduced survival and treatment-response rates compared to patients without the abnormality. About 20% to 50% of all adult cases of ALL are Ph+.^{4,7,9}

The Philadelphia chromosome results in the formation of the BCR-ABL fusion gene mutation. The ABL (Abelson) gene is located on chromosome 9 and encodes for a particular tyrosine kinase and it can fuse with the breakpoint cluster region (BCR) on chromosome 22 to form the BCR-ABL fusion gene, resulting in unregulated tyrosine kinase activity.³ The expression of BCR-ABL mutations confer a dismal prognosis in adult Ph+ patients.⁹ The BCR-ABL mutation occurs in 20% of adult patients with ALL and > 50% of ALL patients aged > 50 years.⁸

CURRENT OR CONVENTIONAL THERAPY

The approach to therapy for adults is along similar lines to those employed successfully in children: an induction course of one or more phases is followed by two or more consolidation periods and treatment directed at the CNS, followed by long-term maintenance for up to three years.²

The initial phase is called remission induction and aims to rapidly reduce the number of leukaemic cells in the body. This phase typically lasts between three and eight weeks of inpatient treatment.¹

Initially, at least three drugs are used in combination to increase the cytotoxic effect, improve remission rates, and reduce the frequency of emergence of drug resistance. Induction chemotherapy usually consists of an oral corticosteroid (prednisolone or dexamethasone), vincristine, an anthracycline (particularly daunorubicin), and asparaginase (crisantaspase).^{2,7} These combinations can be expected to achieve a remission for > 75% of all patients.^{1,7}

In order to eliminate the residual leukaemic cell population induction chemotherapy is followed by course of consolidation therapy.² This therapy, sometimes also referred to as post-induction or post-remission therapy,¹ may consist of chemotherapy alone or a combination of chemotherapy, radiotherapy, and bone marrow transplantation.

The chemotherapy component mainly consists of rotational cycles of different cytotoxic drugs including those used for induction with the addition of cytarabine, etoposide, thioguanine, methotrexate, or mercaptopurine.²

Patients with ALL are at high risk of developing metastatic disease in the central nervous system (CNS). Standard doses of many drugs cannot reach leukaemic cells in the CNS and so high systemic doses of cytarabine or methotrexate are used to eradicate these cells. These drugs will often be introduced during the induction phases.²

Following induction and consolidation therapy, long-term maintenance chemotherapy is given for two to three years with the aim of sustaining complete remission. Therapy will usually consist of daily oral mercaptopurine, weekly oral methotrexate, monthly vincristine, and short five-day courses of oral corticosteroids.^{1,2}

Relapse can occur in a variety of sites including the testes, CNS, and bone marrow.

Stem cell transplantation (SCT) plays an important role in the management of those patients who fail chemotherapy or are at risk of doing so.² SCT is not used routinely in the treatment of adult ALL but may be appropriate for high- and standard-risk patients in their first complete remission, or patients who subsequently relapse following remission.¹

Recently a new class of drug, the tyrosine kinase inhibitors, has been incorporated into treatment regimens for Ph+ ALL.^{1,7,8} Imatinib (Glivec[®]▼ tablets, Novartis Pharmaceuticals) was the first to be marketed although newer agents are now available with several others in development.^{3,10}

Tyrosine kinases phosphorylate proteins on tyrosine residues resulting in a biological signal that influences several aspects of cell function, including cell growth, proliferation, differentiation, and death. Constitutive or unregulated over expression of these enzymes is a common feature in many acute and chronic leukaemias. Thus, inhibition of tyrosine kinases represents a useful strategy to disrupt signalling

pathways that promote neoplastic growth and survival in haematological malignancies.¹¹

Currently, for some Ph+ ALL patients, treatment is governed by the medical research council ALL trial XII (UKALL XII).¹² This study is specifically investigating the role of imatinib and bone marrow transplantation in patients with Ph+ ALL. The treatment protocol dictates two induction chemotherapy phases, each of four weeks duration. The first induction phase consists of intravenous daunorubicin, vincristine and asparaginase, and oral allopurinol and high-dose prednisolone. Intrathecal methotrexate is also introduced during this phase. Phase II consists of intravenous cyclophosphamide and cytarabine, and oral mercaptopurine and imatinib (400 to 600 mg daily). Again, intrathecal methotrexate is also administered during this phase. The induction phases are followed by a four-week intensification phase during which imatinib is continued. Treatment then differs depending on whether patients are undergoing an autologous or an allogeneic SCT. For patients undergoing an autologous SCT additional chemotherapy is administered consisting of mitoxantrone and cytarabine, along with lenograstin (a granulocyte-colony stimulating factor). Patients undergoing an allogeneic SCT do not receive any additional chemotherapy. Imatinib treatment is ceased for all patients during this eight-week period, which is immediately followed by SCT. All patients, as preparation for SCT, receive radiotherapy, etoposide and ciclosporin commencing about one week prior to the procedure. After SCT imatinib is recommenced and maintained at 400 to 600 mg daily until relapse. Other drugs will be used during the maintenance phase as per standard treatment as indicated.

DASATINIB

Dasatinib (Sprycel[®]▼, Bristol-Myers Squibb) is an oral tyrosine kinase inhibitor with some pharmacology distinct from imatinib. For example, dasatinib also inhibits the sarcoma virus oncogene (SRC) family of kinases and other selected oncogenic kinases.¹³ Dasatinib is structurally distinct from imatinib enabling it to bind to active and inactive forms of BCR-ABL kinase and potentially making it less susceptible to structural mutations that confer drug resistance.^{14,15}

Dasatinib is licensed for the treatment of adults with chronic, accelerated or blast-phase chronic myeloid leukaemia (CML) with resistance or intolerance to prior therapy, including imatinib, and the treatment of adults with Ph+ ALL and lymphoid blast CML with resistance or intolerance to prior therapy.¹³

The purpose of this report is to evaluate the efficacy and safety of dasatinib in the management of Ph+ ALL in adult patients.

EFFICACY

The evidence base for the use of dasatinib in patients with ALL is not fully developed and the available evidence consists of a sub-group of patients from a large phase I study, interim results of a specific phase II study, and data in abstract from a phase III dose-ranging study.

Talpaz et al conducted an open-label, phase I, dose-escalation study in 84 patients with CML or Ph+ ALL who were imatinib-resistant or intolerant.¹⁶ The study commenced in November 2003 with final patient enrolment in April 2005. This summary is based on evidence published in June 2006 and focuses on the sub-group of ten patients identified as having either CML with lymphoid blast crisis (n = 5) or Ph+ ALL (n = 5). The median age of the patients was 50 years (range 15 to 73), and only one was female. Median disease duration was 26 months (range 9 to 70). All had previously been treated with imatinib, with seven receiving a dose of > 600 mg daily. The reasons for imatinib failure were: primary resistance (n = 1), secondary (acquired) resistance (n = 8), and intolerance not specified (n = 1). Nine had demonstrated a complete haematological response to imatinib but only three had demonstrated a cytogenetic response. Other previous treatments included: bone marrow or stem-cell transplant (n = 5), any chemotherapy (n = 9), and interferon (n = 2). Patients were treated with dasatinib (dose range 35 to 120 mg twice daily) initially for repeated cycles consisting of five days on treatment followed by two days off; progression to continuous daily doses was permitted. Three patients required dose interruptions, one required a dose reduction and one required a dose escalation. The primary objective of the study was to define the tolerability and safety of dasatinib, and secondary end points related to pharmacokinetic, efficacy, and morphological parameters. Nearly all of the patients with blast crisis CML or Ph+ ALL had a relapse within six months and one went on to receive an allogeneic stem cell transplant. Of the five patients with ALL one each of the following results were recorded: a partial cytogenetic response, a complete haematological and partial cytogenetic response, a complete haematological and complete cytogenetic response, 'no evidence of leukaemia' on haematological screening and a minor cytogenetic response, and no response at all.

Ottmann et al reported interim results with a minimum follow-up of eight months from the START-L phase II study in the sub-group of 36 patients with Ph+ ALL. The study also recruited patients with CML, but the results reported here relate only to the 36 ALL patients.¹⁷ Patients had a mean age of 46 years (range 15 to 85), and 64% were male. Median disease duration was 20 months (range 3 to 97). All patients had previously received imatinib \geq 400 mg daily with 47% receiving > 600 mg daily. Reasons for imatinib failure were: resistance (94%), and intolerance (6%, 2 patients). Patients had also received other previous treatments: chemotherapy (89%), interferon (8%), and SCT (42%). Following the findings of the study by Talpaz¹⁶ all patients were treated with continuous-dose dasatinib 70 mg twice daily with adjustments permitted based on response and toxicity. The primary outcome measures were the rates of major and overall haematological responses. Secondary outcome measures included duration of response, cytogenetically determined response rates, and safety and tolerability. The overall haematological response rate was 50% with 42% recording a major haematological response (33% complete response and 8% 'no evidence of leukaemia' on haematological screening). Consequently, no haematological response was observed in the remaining 50% of patients. In terms of cytogenetic responses, 58% recorded a complete response, one

patient recorded a minor response, and the remainder discontinued therapy before the first cytogenetic assessment scheduled at one month. There were no negative, minimal, or partial cytogenetic responses. The median duration of therapy was 3.2 months (range 0.2 to 11.0) although at the time of publication nine patients were still receiving treatment. Median progression-free survival was 3.3 months. Most patients who discontinued did so due to disease progression (n = 17). Additionally, four died, three underwent SCT, two could not tolerate therapy, and one deteriorated without progression.

A further follow-up of the START-L population with Ph+ ALL was presented at the 48th American Society of Hematology conference in 2006. This included 46 patients with Ph+ ALL with follow-up ranging from 0 to > 18 months.¹⁸ The results for this cohort are broadly in line with the results for the patients reported in the published interim analysis. Improved cytogenetic response rates in patients who had a prior SCT were observed with median survival of 9 months, compared to 5.8 months without prior-SCT. The overall median survival was 8 months. The median mean daily dose was 143 mg (range 83 to 180 mg), with 30% of patients experiencing a dose reduction, 43% dose interruption, and 59% dose escalation. After one year, 22% of patients were alive and progression free, with median progression-free survival of 3.7 months.

A large phase III dose optimisation study (CA180-035), reported in abstract only, compared dasatinib 140 mg once daily (n = 304) to 70 mg twice daily (n = 305), with dose adjustments permitted depending on toxicity and efficacy.¹⁹ The study population included 84 patients with Ph+ ALL (n = 40 and 44 respectively) who were resistant to, or intolerant of, imatinib. In the overall patient population (n = 611),²⁰ 56% were male and the median age was 55 years.¹⁹ The primary outcome measure was the difference in haematological response rates between the two treatment groups.¹⁹ After a median follow-up of 6.5 months for the overall trial population (range < 1 to 17) the Ph+ ALL patients (once daily and twice daily respectively) demonstrated major haematological response rates of 38% and 32% and major cytogenetic response rates of 68% and 55% including complete cytogenetic responses in 50% and 37%.¹⁹ The median progression-free survival in patients with Ph+ ALL using the twice daily regimen was about 3 to 3.5 months.²⁰

RESISTANCE TO DASATINIB

Although BCR-ABL mutations resistant to dasatinib occur less frequently than those to imatinib, specific resistance to dasatinib has been reported.²¹⁻²⁴ As yet it is not possible to predict the occurrence of resistance and no effective strategies to overcome resistance to dasatinib are available. It appears that re-treatment with imatinib or increasing the dose of dasatinib are not effective strategies.²²⁻²⁴

ADVERSE EFFECTS

In the phase I study by Talpaz et al the most common adverse effects affecting the ten patients with blast-phase CML or Ph+ ALL were grade ≥ 3 neutropenia (n = 8), grade 4 thrombocytopenia (n = 7), grade ≤ 2 diarrhoea (n = 2), grade ≤ 2 pleural effusion (n = 2), and one report for each of (all grade ≤ 2) nausea, vomiting, peripheral oedema, periorbital oedema, general oedema, dyspnoea or pulmonary oedema, rash, and fatigue. At baseline these patients already had a high incidence of grade ≥ 3 neutropenia (20%) and grade ≥ 3 thrombocytopenia (70%).¹⁶

The most common adverse effects of all grades of severity (and grades 3 and 4 only) observed in the START-L study with eight months of follow-up (n = 36) are displayed in table 1.¹⁷

Table 1. Most frequent adverse effects observed in the START-L study

Adverse effect	Incidence (all grades, n)	Incidence (grades 3 and 4, n)
Diarrhoea	11	3
Pyrexia	9	1
Nausea	8	0
Asthenia	7	3
Pleural effusion	7	1
Rash	6	1
Peripheral oedema	6	0
Weight loss	6	0
Dyspnoea	5	1
Febrile neutropenia	4	4

Safety data relating to the unpublished study CA180-035 are available in the summary of product characteristics for Sprycel[®] and in the published abstract, but are not broken down by leukaemia sub-group. The most common adverse effects for once daily (n = 304) vs. twice daily (n = 305) regimens are reported in table 2.^{13,19} Other less frequent outcomes relating to fluid retention affected patients using the twice-daily regimen more frequently than those using the once-daily regimen, for example pericardial effusion, pulmonary oedema, ascites, and pulmonary hypertension.^{13,20}

Table 2. Most frequent adverse effects observed in study CA 180-035

Adverse effect	Incidence (all grades)		Incidence (grade 3 and 4)	
	Once daily	Twice daily	Once daily	Twice daily
Thrombocytopenia	89%	92%	68%	70%
Neutropenia	85%	87%	65%	70%
Diarrhoea	27%	27%	3%	3%
Fluid retention	26%	34%	5%	9%
Superficial oedema	12%	16%	< 1%	1%
Pleural effusion	16%	23%	5%	6%
Gastrointestinal bleeding	7%	12%	6%	6%

DOSAGE, ADMINISTRATION AND COST

Dasatinib is available as 20, 50 and 70 mg tablets in packs of 56. The recommended starting dose in Ph+ ALL is 70 mg twice daily with a recommended maximum dose of 100 mg twice daily.¹³ Treatment should be continued until disease progression occurs or until no longer tolerated by the patient. The cost for one pack of 70 mg tablets is **£2,432.85**.

In the START-L study the median duration of treatment was 3.2 months, about 14 weeks,¹⁷ which is similar to the median progression-free survival obtained in Ph+ ALL patients treated with dasatinib 70 mg twice daily in study CA180-035.²⁰ The cost for 14 weeks treatment is **£8,515**. The maximum duration of treatment in the START-L study was 11 months and at the time of publication patients were still receiving therapy.¹⁷ Nonetheless, the cost for 11 months of treatment is about £28,500.

There are few additional costs associated specifically with dasatinib: some patients can be expected to experience excessive myelosuppression which may result in increased need for supportive therapy such as blood transfusions and haematopoietic agents (e.g. granulocyte-colony stimulating factor and erythropoietin) although these patients are already at risk of increased requirements for such supportive therapy.¹⁷ Other additional costs stemming from treating the adverse effects of dasatinib include, for example, oedema including pulmonary oedema and pleural effusions, which may require pharmacological management with diuretics and corticosteroids or in serious cases hospitalisation.¹³ It has not been possible to accurately factor for these costs.

The annual incidence of adult ALL is about 1.6 per 100,000 of the population.⁶ It may be assumed that 30% of patients will be Ph+²⁵ and all will eventually become resistant or intolerant to imatinib and progress to treatment with dasatinib. In this scenario the cost of treating these patients with dasatinib for a median of 14 weeks is around £4,100 per 100,000 population per annum.

Some of the cost of dasatinib can be offset by the cost of imatinib treatment. The incremental cost of dasatinib 70 mg twice-daily compared to imatinib 400 mg daily is £936 per four weeks. Most patients recruited in the dasatinib studies had previously been treated with imatinib \geq 600 mg daily. The incremental cost of dasatinib 70 mg twice-daily for four weeks compared to imatinib 600 mg daily is £185.

In the UKALL XII study imatinib is provided at no cost,¹² therefore a change in therapy to dasatinib may have a substantial impact on the cost of treating patients with Ph+ ALL as the offset cost will be nil.

These costs do not include VAT or any locally negotiated discounts.

PLACE IN TREATMENT

The evidence base for dasatinib in ALL comprises data from only 125 patients (five from a phase I study, 36 from an interim report of a phase II study and 84 from abstract data of a phase III study). No studies included a non-dasatinib-treated arm, and there have been no comparisons with best supportive care. These are major limitations to a rigorous assessment of dasatinib for ALL. All the patients in these studies were imatinib-resistant or intolerant for whom the alternative treatment option would be best supportive care. The benefits of treatment with dasatinib were substantial in some patients but were limited in the majority, with patients ceasing treatment after a median of just 3.2 months and progression-free survival lasting a median of about 3.5 months. There are no comparative studies against placebo or non-dasatinib active treatments in Ph+ ALL patients. Dasatinib is an expensive therapy with uncertain benefits in this patient group, and it increases the burden of morbidity in patients who may be close to death. It is not clear how dasatinib will fit into treatment protocols, particularly with respect to the UKALL XII study.

Neither the Scottish Medicines Consortium (SMC) nor the All Wales Medicines Strategy Group have recommended dasatinib for Ph+ ALL and in both instances it was determined that the case for cost effectiveness was not sufficiently robust.^{26,27} As part of the submission to the SMC it was estimated that the cost per quality adjusted life year gained for Ph+ ALL patients would be the same as that for patients with blast-phase CML, at £64,000.²⁶

The National Institute for Health and Clinical Excellence has included dasatinib for Ph+ ALL as part of their 17th wave of technology appraisals, however their determination is unlikely to be available before 2009.²⁸

Dasatinib is not a cost-effective treatment option if provided to all patients with ALL who meet the licensed criteria and therefore its use is not recommended except in patients who are expected to derive the most benefit. Currently the available evidence does not permit the accurate identification of those patients and therefore the use of dasatinib for adult patients with Ph+ ALL is not recommended.

ARRANGEMENTS FOR PRESCRIBING

Prescribing and monitoring should remain under the care of specialists experienced in the treatment of haematological malignancies.

FUTURE DEVELOPMENTS

Nilotinib was developed by the same company that developed imatinib, and it overcomes some of the more frequent mutations that confer imatinib resistance. Nilotinib became available in May 2008 but it is not currently licensed for the treatment of ALL.²⁹ Several other kinase inhibitors are currently in development.⁷

ACKNOWLEDGEMENTS

We are grateful to the following people for helpful advice and comments in the preparation of this report. The Regional Drug and Therapeutics Centre accept final responsibility for the content of this document.

Dr G Jackson	Clinical Director of Haematology, <i>and</i> Honorary Clinical Reader in Clinical Haematology	Newcastle Upon Tyne Hospitals NHS Trust Newcastle University
Mr D Thomson	Lead Pharmacist	Yorkshire Cancer Network
Mr S Williamson	Consultant Pharmacist in Cancer Services	North of England Cancer Network

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SUMMARY TABLE OF KEY STUDIES

Key: ALL – acute lymphoblastic leukaemia, CML – chronic myeloid leukaemia, ECOG – Eastern Co-operative Oncology Group, MC – multicentre, OL – open label, P1 – phase one, P2 – phase two, P3 – phase 3, Ph+ – Philadelphia chromosome-positive

Reference	Design	Intervention	Patient numbers	Inclusion criteria	Exclusion criteria	Primary outcome	Results	Adverse effects
Talpaz et al. ¹⁶	OL, P1, dose-escalation	Dasatinib 35 to 120 mg twice daily,* initially for five days followed by two days off-treatment in repeated cycles but subsequently in continuous daily dosing	84 patients with imatinib-resistant CML or Ph+ ALL. *Ten patients were identified with Ph+ ALL or CML with lymphoid blast crisis and were treated with these doses	Age ≥ 14 years Ph+ chronic or accelerated phase CML or blast-phase CML or Ph+ ALL, and haematological resistance or intolerance to imatinib	Cytogenetic or molecular resistance to imatinib	None defined. Primary objective was to investigate the tolerability and safety of dasatinib	Of the five patients with Ph+ ALL: One partial cytogenetic response One complete haematological and partial cytogenetic response One complete haematological and complete cytogenetic response One 'no evidence of leukaemia' on haematological screening and minor cytogenetic response One no response at all	Adverse effects reported in patients with CML with lymphoid blast crisis, or Ph+ ALL (n = 10): Generalised oedema (1), dyspnoea or pulmonary oedema (1), rash (1), fatigue (1), neutropenia (8 [6 with grade 4 neutropenia]), grade 4 thrombocytopenia (7), diarrhoea (2), nausea (1), pleural effusion (2), peripheral oedema (1), periorbital oedema (1)

Reference	Design	Intervention	Patient numbers	Inclusion criteria	Exclusion criteria	Primary outcome	Results	Adverse effects
Ottmann et al. ¹⁷ (CA180-015 START-L study)	OL, P2, MC	Dasatinib 70 mg twice daily (dose adjustments permitted depending on efficacy and toxicity)	36 Ph+ ALL patients resistant to, or intolerant of, imatinib	Age ≥ 18 years ECOG performance status ≤ 2	Prior dasatinib therapy, recent (≤ 7 days) imatinib therapy, uncontrolled or significant cardiovascular disease, significant bleeding disorder unrelated to ALL	None defined Primary objectives were to establish the rates of major haematological and overall haematological response	With a minimum follow-up of eight months: 15 patients (42%) achieved a major haematological response, 10 of whom remained progression free The overall haematological response rate was 50% (18 patients)	Proportion of patients affected (grade 3 or 4 severity): Diarrhoea 31% (8%), pyrexia 25% (3%), nausea 22%, asthenia 19% (8%), pleural effusion 19% (3%), rash 17% (3%), weight loss 17%, peripheral oedema 17%, dyspnoea 14% (3%), headache 14%, febrile neutropenia 11% (11%), fatigue 11%, vomiting 11%
Dombret et al. ¹⁸ (CA180-015 START-L study)			46 Ph+ ALL patients resistant to, or intolerant of, imatinib				Major haematological response: 41% Major cytogenetic response: 57%	Pleural effusion 24% (7%), peripheral oedema 13% (0%), pericardial effusion 4% (0%), pulmonary oedema 0%.
Pasquini et al. ^{19,20} (CA180-035)	P3, OL, RC, dose-optimisation study	Dasatinib 140 mg once daily or 70 mg twice daily (dose adjustments permitted depending on efficacy and toxicity)	611 in total, 84 with Ph+ ALL: 40 dosed once daily and 44 dosed twice daily	Imatinib resistant or intolerant advanced phase CML or Ph+ ALL		Major haematological response rate	Ph+ ALL patients only. Major haematological response: Once daily – 38% Twice daily – 32% Major cytological response: Once daily – 68% Twice daily – 55% Complete cytological response: Once daily – 50% Twice daily – 37%	Affecting all patients randomised to twice daily dosing (n = 305). Proportion of patients affected (grade 3 or 4 severity): Pleural effusion 27% (7%), peripheral oedema 14% (1%), pericardial effusion 4% (2%), pulmonary oedema 3% (1%) Dose interruption 57%, dose reduction 39%

