Greater Manchester and Cheshire Cancer Network

Chronic Myeloid Leukaemia v3 2012

Dr Simon Watt
Dr Shiva Natarajan

1.0 Introduction

The landscape in chronic myeloid leukaemia (CML) has changed dramatically in the last decade with the advent of tyrosine kinase inhibitors. Median survival has increased to an estimated 25-30 years.
There is still debate on the best treatment and not all patients will have optimal response to their treatment. This document will attempt to draw together and summarise current guidelines research and opinion around CML.

The contribution of Prof Richard Clark's recent updated guidance is gratefully acknowledged.

2.0 Initial assessment

This should include the spleen size (measured as a perpendicular line between the costal margin and the spleen tip), presentation peripheral blood platelet, eosinophil, basophil and platelet count and peripheral blood blast cell count. These, together with age will enable the Sokal and Hasford (EUROscore) prognostic risk groups to be calculated (Hehlman R et al, Lancet 370, 342-350, 2007), although these will rarely influence initial treatment decisions.

Sokal score = Exp[0.0116 (age−43.4 years)
+0.0345 (spleen size−7.51)
+0.188 ([platelets/700]2−0.563)+0.0887 (blasts−2.1)]

Low risk <0.8 Intermediate risk 0.8–1・2 High risk >1.2

Hasford score = (0.6666×age [0 when age <50 years; otherwise 1]+0・042
×spleen size (cm below costal margin)+0・0584×blasts [%]+0・0413
×eosinophils [%]+0・2039
×basophils [0 when basophils <3%;otherwise 1]+1・0956
×platelet count [0 when platelets<1500 per μL; otherwise 1])×1000

Low risk <780
Intermediate risk 780–1480
High risk >1480

Cytogenetic analysis is essential to diagnose the t(9;22) translocation, or Philadelphia chromosome. This distinguishes typical CML from Philadelphia negative types and reactive marrows. For the 5% of cases with morphologically typical CML but normal cytogenetics, bone marrow FISH for BCR-ABL will permit cryptic BCR-ABL rearrangements to be detected. Peripheral blood (or bone marrow) BCR-ABL analysis by RQ-PCR is also advised at diagnosis, since rarely it is the only confirmatory test. In addition it is helpful to know that RQ-PCR has detected BCR-ABL at presentation, to give greater confidence in subsequent tests monitoring response to treatment.

Patients lacking the Philadelphia chromosome, and negative by both FISH and RQ-PCR for BCR-ABL do not have CML and should not be offered imatinib.

Although the diagnosis of CML does not specifically require bone marrow cytogenetic analysis, it should always be performed at diagnosis, as additional chromosome abnormalities of prognostic significance may be present at diagnosis.

Cytogenetic analysis and FISH are performed by the Cytogenetics Laboratory at the Christie Hospital. RQ-PCR for BCR-ABL can be performed on 10 ml EDTA-anticoagulated blood sent by first class post to Molecular Genetics Lab, Department of Haematology, CMFT
Accelerated phase as defined by WHO.

1) Increasing WBC (>10) or splenomegaly unresponsive to therapy
2) Persistent thrombocytosis (>1000) unresponsive to therapy
3) Persistent thrombocytopenia (<100) unrelated to therapy
4) Clonal cytogenetic evolution
5) 20% or more basophils in the PB
6) 10-19% myeloblasts in the PB or BM

However these definitions are not universally accepted- for example the criteria for SPIRIT 2 is modified There are no reliable criteria for accelerated phase based on a low platelet count, as it is virtually impossible to distinguish the effects of treatment from the effects of accelerating disease. Acquisition of additional chromosome abnormalities, beyond a single Ph chromosome, is NOT considered to define disease progression.

Blast crisis is defined as blasts in the blood or bone marrow of greater than or equal to 20%, or the appearance of extramedullary involvement (e.g. chloromas), except for hepatosplenomegaly. It is important to determine by morphology and immunophenotyping of the blood and marrow whether the acute phase is myeloid (approx 70%) or lymphoid (approx 30%). Myeloid acute phase may be treated with schedules appropriate for AML.

3.0 Initial management of chronic phase CML

Leucapheresis should be used to reduce the white cell count rapidly if there are signs of impending leucostasis (e.g. deteriorating level of consciousness, papilloedema, retinal venous engorgement/haemorrhages, or priapism). Leucapheresis and cryopreservation can also be considered before treatment is started for younger (<60 years) patients who may subsequently be candidates for stem cell transplantation as a back up for a future allograft. Harvests taken at diagnosis are preferable to those taken later in the disease, since at diagnosis there is still a high proportion of circulating normal stem cells. If a patient is likely to require leucapheresis, early discussion with a Centre (Dr Dignan at MRI, Dr Dennis at the Christie Hospital) offering this facility is advisable if appropriate.

If active treatment is required while confirmation of diagnosis is awaited, Hydroxycarbamide (Hydroxyurea) can be used to reduce the white cell count. It is usually well tolerated, although gastrointestinal symptoms may occur, particularly with higher doses. The initial dose is 1.5 - 2 g/day orally which is then adjusted to keep the WCC in the normal range. During periods of active cell lysis, Allopurinol 300 mg/day should be given and an adequate intake of fluids maintained.

3.1Definitive treatments

All patients will be discussed in the relevant local haematology MDT.

Where available patients should be offered a clinical trial. At the time of writing the SPIRIT2 trial is widely available nationally. This is a NCRN phase III study comparing imatinib with dasatinib, each at standard dosage. It is anticipated that SPIRIT 2 will complete recruitment by April 2013, it is intended that a “SPIRIT3” trial will open later in 2013.

Patients not wishing enrol/ineligible for clinical trials should be offered a tyrosine kinase inhibitor as first line therapy.

TKI with first line EMEA license
Imatinib 400mg daily
Nilotinib 300mg BD
Dasatinib 100mg daily

Currently there is longest follow up with imatinib with 8 year data in the IRIS study presented at ASH in 2009. The 3 year data in the DASISON (dasatinib v imatinib) and ENESTnd (nilotinib v imatinib) trials were recently presented at EHA 2012. They do not show any improvement in overall survival over imatinib, but do show more rapid and deeper molecular responses and a reduction in rates of transformation to accelerated phase and blast crisis. To date it isn’t clear if this will translate to better outcomes in the long term.

NICE have recently approved nilotinib for first line use, provided it is dispensed in line with the manufacturer’s discount scheme (NICE TA251).

http://publications.nice.org.uk/dasatinib-nilotinib-and-standard-dose-imatinib-for-the-first-line-treatment-of-chronic-myeloid-ta251 (accessed 16/11/2012)

Nilotinib should therefore be available to all haematologists. Dasatinib was not approved for first line usage, but may be available through the cancer drugs fund or individual funding requests for patients resistant/intolerant or unsuitable for imatinib or nilotinib (due to toxicity profile). There are differences in the drugs in side effects and how the drugs are taken. For further information the SPC of the drugs should be consulted at www.medicines.org.uk .

Physicians may also wish to take into account that the patent on imatinib will expire in 2016 potentially resulting in cost savings for the NHS.

First line therapy with SCT is no longer justifiable for any adult patient in chronic phase, and paediatric patients are increasingly also treated with TKI as first-line therapy.

4.0 Management of advanced phase disease

Advanced disease comprises accelerated phase and blast crisis.

Accelerated Phase

In the absence of any available trial, the optimal management of accelerated phase is imatinib with a starting dose of 600mg daily. Patients who respond well should be considered for early SCT if this is otherwise appropriate.

Nilotinib 400mg bd and dasatinib 140mg daily are licensed for second line treatments in advanced stage disease however only nilotinib has NICE approval for this indication (TA241)

http://guidance.nice.org.uk/TA241 (accessed 16/11/2012)

Blast crisis

It is important to determine by morphology and immunophenotyping,whether the acute phase is myeloid or lymphoid. Similar TKI therapies to those for AP can be tried in TKI naïve patients presenting in blast crisis. Myeloid acute phase may be treated with schedules appropriate for AML, and FLAG-IDA is widely used. FLAG-IDA may also be appropriate in lymphoid transformation, where standard intrathecal treatment should also be considered, as for *de novo* acute lymphoblastic leukaemia, consideration should be given to adding in a TKI.
The patient should also be considered for suitability for allografting early in the management of the disease as otherwise prognosis is very poor

If patients are not suitable for this, imatinib 600 mg daily may produce a second chronic phase in about 15% of patients, though responses are improved if this is given with conventional acute leukaemia therapy. Dasatinib 140mg daily has not been approved by NICE but if AML-style chemotherapy is not feasible then it may be appropriate where patients progress into blast crisis while already on imatinib. Nilotinib is not licensed in blast crisis though may be of some short term benefit.

5.0 Monitoring of patients on TKIs

For monitoring progress in chronic phase, a combination of blood counts, marrow cytogenetics and peripheral blood molecular monitoring should be used. The first goal of treatment is to achieve a normal blood count and resolution of any splenomegaly. This is the definition of a complete haematological response (CHR), and is achieved in at least 95% of patients with any of the 3 licensed TKI (imatinib, dasatinib and nilotinib) within 6 weeks. The second goal of treatment is to achieve clearance of the Ph chromosome from the marrow, assessed on at least 20 conventional metaphase cytogenetic spreads. This is known as complete cytogenetic response (CCR), and ideally should be achieved within 12 months; it may however be reasonable to allow 'slow responders' up to 18 months to achieve CCR.

Molecular monitoring of BCR-ABL1 at 3 monthly intervals is generally used to monitor response, and is available at Molecular Genetics Lab at CMFT. This measures the ratio of BCR-ABL1 (leukaemic) to ABL1 (normal) transcripts by real time PCR, and is expressed as a percentage. Several groups have shown that the threshold of complete cytogenetic response correlates very well with a BCR-ABL1/ABL1 percentage of 1%; molecular monitoring alone may therefore be adequate for patients who decline a marrow examination for CCR assessment at 12+ months of treatment. A third target for treatment is a BCR-ABL1/ABL1 ratio of 0.1%; this is known as major molecular response (MMR). Although patients who achieve MMR have an exceptionally low rate of disease progression (zero in IRIS), it is not yet clear how essential it is to achieve MMR, provided the patient has achieved CCR; it is currently therefore not clear whether to set MMR as a third and essential goal of treatment. Finally, about 5-10% of patients may achieve a so called 'complete' molecular response (CMR), defined as no detectable BCR-ABL1 transcripts in a sample with at least 10,000 (sometimes 30,000) ABL1 transcripts. A better nomenclature may be 'Molecular response at 4 logs' (MR4) or 4½ logs (MR4.5). There is current interest in whether patients who are persistently in MR4 or even MMR can safely stop their TKI; this is not advisable outside of a clinical trial.

Summary of suggested monitoring

Test	Frequency
FBC	2 weekly until CHR then 3 monthly
Cytogenetics/FISH on bone marrow	At diagnosis then at 1 year. Further testing if no CCR or possible loss of response to TKI
PCR on peripheral blood	3 monthly until MMR then 6 monthly

6.0 Treatment failure or intolerance on 1st line TKIs

The following table is adapted from the European Leukemia Net (Baccarani et al, 2009) 2009 guidelines which updated the previous 2006 guidelines:

New recommendations are marked in yellow.

Time	Optimal response	Suboptimal response	Failure	Warnings
Diagnosis	N/A	N/A	N/A	High Risk CCA/Ph+[3]
3 mon.	CHR, at least Minor CgR	No CgR	Less than CHR	N/A
6 mon.	At least PCgR	Less than PCgR	No CgR	N/A
12 mon.	CCgR	PCgR	Less than PCgR	Less than MMR
18 mon.	MMR	Less than MMR	Less than CCgR	N/A
Any time (during treatment)	Stable or improving MMR	Loss of MMR Mutations[1]	Loss of CHR, Loss of CCgR, Mutations[2] CCA/Ph+[3]	Increase in transcript levels CCA/Ph-

mon.: Months after diagnosis **N/A:** Not applicable **CCA:** Clonal chromosome abnormalities

[1] BCR-ABL1 kinase domain mutations still sensitive to imatinib, [2] BCR-ABL1 kinase domain mutations poorly sensitive to imatinib or other TKIs, [3] CCA/Ph+ is a "warning" factor at diagnosis, although its occurrence during treatment (i.e., clonal progression) is a marker of treatment failure. Two consecutive cytogenetic tests are required and must show the same CCA in at least two Ph+ cells.

The ELN 2009 guidelines recommend that patients with imatinib failure can be treated with a second generation TKI. Both dasatinib and nilotinib are licensed for use in imatinib failure or intolerance. NICE have not approved dasatinib for use in either first line (TA251) or second line (TA241), principally because it now costs the NHS about 50% more than either nilotinib or imatinib. Approximately 12% of patients may develop pleural effusions on dasatinib, and about 1% of patients may develop pancreatic problems on nilotinib. These drugs may therefore be best avoided in patients with cardiorespiratory or pancreatic problems respectively. Dose escalation of imatinib may achieve some short term benefits but these are rarely durable and is not recommended; furthermore NICE have not approved this approach (updated TA70).

http://guidance.nice.org.uk/TA241 (accessed 16/11/2012)

The evidence above is based on treatment with imatinib and it isn't clear if the same response points can be used for other TKIs. In the absence of other data it seems reasonable to use the above for a guide for treatment failure in nilotinib and dasatinib also.

References

Baccarani M, **Cortes** J, **Pane** F, Niederwieser D, Saglio G, Apperley J, Cervantes F, Deininger M, Gratwohl A, Guilhot F, Hochhaus A, Horowitz M, Hughes T, Kantarjian H, Larson R, Radich J, Simonsson B, Silver RT, Goldman J, Hehlmann R; European LeukemiaNet. Chronic myeloid leukemia: an update of concepts and management recommendations of European LeukemiaNet. J Clin Oncol. 2009 Dec 10;27(35):6041-51. Epub 2009 Nov 2. Review

Kantarjian H, Shah NP, Hochhaus A, Cortes J, Shah S, Ayala M, Moiraghi B, Shen Z, Mayer J, Pasquini R, Nakamae H, Huguet F, Boqué C, Chuah C, Bleickardt E, Bradley-Garelik MB, Zhu C, Szatrowski T, Shapiro D, Baccarani M. **Dasatinib** versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med. 2010 Jun 17;362(24):2260-70. Epub 2010 Jun 5.

Larson RA, Hochhaus A, Hughes TP, **Clark** RE, Etienne G, Kim DW, Flinn IW, Kurokawa M, Moiraghi B, Yu R, Blakesley RE, Gallagher NJ, Saglio G, Kantarjian HM. Nilotinib vs imatinib in patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase: ENESTnd 3-year follow-up. Leukemia. 2012 Oct;26(10):2197-203. doi: 10.1038/leu.2012.134. Epub 2012 May 18.

Saglio G, **Kim** DW, **Issaragrisil** S, le Coutre P, Etienne G, Lobo C, Pasquini R, Clark RE, Hochhaus A, Hughes TP, Gallagher N, Hoenekopp A, Dong M, Haque A, Larson RA, Kantarjian HM; ENESTnd Investigators. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia.N Engl J Med. 2010 Jun 17;362(24):2251-9. Epub 2010 Jun 5.

http://publications.nice.org.uk/dasatinib-nilotinib-and-standard-dose-imatinib-for-the-first-line-treatment-of-chronic-myeloid-ta251

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