

# Managing children with chronic myeloid leukaemia (CML)

## Recommendations for the management of CML in children and young people up to the age of 18 years

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### Summary

Chronic myeloid leukaemia in children and young people is a relatively rare form of leukaemia that shows increased incidence with age and some evidence suggests that the molecular basis differs from that in adults. Significant advances in targeted therapy with the development and use in children of tyrosine kinase inhibitors and the ability to monitor and understand the prognostic significance of minimal residual disease by standardized molecular techniques has shifted the management of this condition from bone marrow transplantation as the main therapeutic modality to individualized treatment for each patient based on achieving specific milestones. The physiological changes occurring during childhood, particularly those affecting growth and development and the long-term use of treatment, pose specific challenges in this age group, which we are only beginning to understand.

**Keywords:** chronic myeloid leukaemia, children, tyrosine kinase inhibitor, stem cell transplantation, *BCR-ABL1*.

Chronic myeloid leukaemia (CML) constitutes 2–3% of leukaemias in children and has an incidence of 0.6–1.2/million children/year. Its incidence increases with age: it is exceptionally rare in infancy, 0.7/million children/year for patients aged 1–14 years and 1.2/million children/year in adolescents. As in adults, there is an increased prevalence in males (1.2:1). The median age at presentation is 11 years. Children tend to present with higher white blood cell counts (WBC) than adults, with a median WBC of  $242 \times 10^9/l$  (Millot *et al*, 2005). Approximately 10% of cases present in advanced

phase, a higher proportion than reported in adults (Suttorp & Millot, 2010).

Although there is some evidence that the molecular basis of CML in children may be different from that in adults (Krumbholz *et al*, 2012), limited data (Cwynarski *et al*, 2003; Millot *et al*, 2005) indicate that 90–95% of children that present with clinical and morphological features of CML are Philadelphia chromosome-positive (Ph<sup>+</sup>), i.e. their haemopoietic cells carry the characteristic reciprocal translocation t(9;22)(q34;q11), which leads to the formation of a *BCR-ABL1* fusion gene and protein. Around half of the remainder also have the *BCR-ABL1* fusion gene despite the absence of a detectable t(9;22) by conventional cytogenetics. The only definite aetiological factor in CML is ionizing radiation (Andolina *et al*, 2012) and there is no clear familial predisposition or link to immune suppression, although isolated case reports have been published of childhood CML in twins (Kosenow & Pfeiffer, 1969), Down syndrome (Cawein *et al*, 1965), after renal transplant (Sanz *et al*, 1996) and in human immunodeficiency virus (HIV) infection (Setty *et al*, 2009).

In the pre-tyrosine kinase inhibitor era, adults with CML treated with hydroxycarbamide or interferon-alpha (IFN- $\alpha$ ) had a median survival in the region of 5 years and a 10-year survival of 5% (Hehlmann *et al*, 1994). The median duration of chronic phase (CP) in haematological remission without imatinib is 4 years (Ozer *et al*, 1993). Once accelerated phase (AP) has developed the median time to transformation to blast crisis (BC) is 6–18 months. Median survival in BC is 3–9 months. The rate of transformation to BC has been estimated at 20–35% per year on hydroxycarbamide/busulphan, 10–20% for patients on IFN- $\alpha$  and 1–1.5% per year for patients on imatinib (Silver *et al*, 1999; Druker *et al*, 2006). The risk of transformation on imatinib is time and response dependent with a decreasing risk of progression and a cumulative incidence AP, BC and death of 5% (Hehlmann *et al*, 2011). There is no evidence that the natural history in

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children is significantly different, although published studies are small (Champagne *et al*, 2004; Millot *et al*, 2005).

This document outlines a suggested management approach for children and young people up to the age of 18 years with CML based where possible on paediatric data, but necessarily relying mainly on data from studies in adults. The aim of these guidelines is to have a uniform management approach and to establish the clinical situations in which novel therapies should be considered, preferably in international clinical trials.

## Diagnostic work up and initial management at presentation

### Confirm diagnosis

Full blood count and blood film	White blood cell (WBC) count Haemoglobin (Hb) and platelet count Basophils % Eosinophils % Monocytes % Blasts % Blasts + promyelocytes %
Bone marrow	Morphology, blast % and promyelocytes % Cytogenetics (for Ph <sup>+</sup> and/or other clonal abnormalities) Fluorescent- <i>in-situ</i> -hybridization (FISH) if marrow cytogenetics fails Trephine biopsy (for fibrosis, cellularity, transformation), but not mandatory Immunophenotyping (if BC)

Other baseline investigations:

- Reverse transcription polymerase chain reaction (RT-PCR) for *BCR-ABL1* (to determine breakpoint in Ph<sup>+</sup> cases for later monitoring and to investigate molecular diagnosis in Ph<sup>-</sup> cases). Results to be expressed according to the international recommendations for harmonizing methodology (Hughes *et al*, 2006)
- tyrosine kinase domain mutation analysis at diagnosis is only indicated for AP/BC
- human leucocyte antigen (HLA)-type patient (high resolution) and family
- blood group
- virology: cytomegalovirus, hepatitis B/C virus, HIV, varicella zoster virus, Epstein–Barr virus
- biochemistry: urea and electrolytes, creatinine, urate, liver function tests, Ca/PO<sub>4</sub>
- coagulation: prothrombin time, activated partial thromboplastin time, thrombin time, fibrinogen
- measure spleen size (cm below the costal margin)
- height
- pubertal development according to Tanner stage
- scoring system (Appendix I)
- samples for research studies

### Determine phase of disease

In addition to accurate diagnosis, the definitive management of CML is based on the phase of the disease at presentation. WHO and European LeukaemiaNet (ELN) have slightly different criteria, the latter (Table I) being the one most used by recent studies (Baccarani *et al*, 2006).

### Immediate management

- treat bleeding/infection, if present
- consider leucapheresis if evidence of leucostasis
- start allopurinol (10 mg/kg; max 300 mg) and ensure good hydration. Allopurinol should only be necessary if the WBC count is >20 × 10<sup>9</sup>/l.
- start hydroxycarbamide 25–50 mg/kg per d as a single daily dose (syrup available) until diagnosis of CML confirmed, if required
- start imatinib once diagnosis confirmed

### Leucapheresis and back-up of autologous cells

There are few data (either paediatric or adult) that specifically address indications for leucapheresis in CML. As with other leukaemias clinical evidence of leucostasis, rather than WBC count, should be the indicator for therapeutic leucapheresis. However, leucostasis is unusual in CML at WBC counts <200 × 10<sup>9</sup>/l. Therapeutic leucapheresis should be carried out as an emergency in patients with leucostasis:

- pulmonary infiltrates
- priapism
- severe retinopathy/papilloedema

Leucapheresis for storing autologous ‘back up’ stem cells is no longer required. Autologous bone marrow cells may still be useful and a bone marrow harvest or peripheral blood stem cell collection may be performed once major molecular

Table I. European LeukaemiaNet (ELN) criteria for disease phase in CML (adapted from Baccarani *et al*, 2006).

Chronic phase	Accelerated phase	Blast crisis
None of the criteria for AP or BC have been met	Blast cells 15–29% in PB or BM Blast cells plus promyelocytes in PB or BM >30%, with blast cells <30% Basophils in blood >20% Persistent thrombocytopenia (<100 × 10 <sup>9</sup> /l) unrelated to therapy	Blast cells ≥30% in PB or BM Extramedullary blast involvement

AP, accelerated phase; BC, blast crisis; BM, bone marrow; PB, peripheral blood.

response (MMR) or if possible, complete molecular remission (CMR) has been achieved (Bashir *et al*, 2010). The main reason for cryopreserving autologous haemopoietic cells in childhood CML is the risk of graft failure following allogeneic blood and marrow transplantation (BMT) or donor lymphocyte infusion (DLI). This occurs in <5% sibling bone marrow transplants; <10% of volunteer unrelated donor BMT and in up to 20% of DLI, if DLI is delayed until haematological relapse. Hence, if BMT is being considered storage of autologous bone marrow cells can be considered at best possible point of response to therapy.

### Cryopreservation of sperm and oocyte vitrification

This should be considered and discussed with all boys of appropriate age and performed at diagnosis. The risk of teratogenicity for boys receiving imatinib appears very low and the current advice is to continue on treatment at the time of conception (Apperley, 2009a). However, there is no data on second generation tyrosine kinase inhibitors (TKIs) and there is no guarantee that the patient will achieve an optimal response, hence avoiding the need to proceed to BMT or second generation (2G) TKI. In addition, there is experimental data from animal studies suggesting that long-term imatinib may lead to reduced testes size and sperm mobility (Nurmio *et al*, 2007).

If possible, sperm collection should occur before the initiation of treatment, particularly before the use of hydroxycarbamide. If this is not possible, it should occur once the patient is on imatinib treatment and at least 3 months after the last dose of hydroxycarbamide.

Oocyte vitrification can be considered in post-menarche young women if BMT is being considered.

### Definitive management of CML

The management of CML is based on the phase of the disease at presentation and response levels (Table II), as these are measures of leukemic cell burden and early surrogate markers of survival (Baccarani *et al*, 2006). Specific response levels must be achieved at determined time-points, milestones, of treatment depending on the TKI used (imatinib or 2G TKI). Specific milestones are discussed in the relevant TKI section. The combination of complete cytogenetic response (CCyR) and partial cytogenetic response (PCyR) constitutes major cytogenetic response. Monitoring should be carried out in certified laboratories only according to harmonized methodology (Hughes *et al*, 2006). Standardized definitions of molecular response should be used (Cross *et al*, 2012).

### Treatment options

#### Imatinib

Imatinib remains the TKI of choice for the initiation of treatment. It is the agent for which more extensive data

**Table II.** Response levels in the monitoring of treatment in CML (adapted from Baccarani *et al*, 2006).

Haematological response (HR)	Cytogenetic response (CyR) Ph <sup>+</sup> metaphases	Molecular response (MR)
CHR	Major	Complete:
WBC <10 × 10 <sup>9</sup> /l	CCyR 0%	Transcripts not detectable in two consecutive samples (sensitivity >10 <sup>4</sup> )
Basophils <5%	PCyR 1–35%	
	Minor 36–65%	Major:
Platelets <450 × 10 <sup>9</sup> /l	Minimal 66–95%	Ratio of <i>BCR-ABL1</i> to <i>ABL1</i> <0.1% (international scale)
Blood film: no myelocytes, promyelocytes or blasts		
Spleen: not palpable		

CHR, complete haematological response; CCyR, complete cytogenetic response; PCyR, partial cytogenetic response; WBC, white blood cells.

exists including the paediatric population, particularly when used as first line therapy. Used in this way, prognostic factors are well understood and allows the generation of time points, milestones, to evaluate the response to treatment. If CCyR is achieved, the pre-treatment risk score of prognostic classifications does not affect the progression-free survival (PFS). In addition, prior treatment with imatinib does not affect negatively the outcome of allogeneic BMT (Lee *et al*, 2008).

*Summary of results with imatinib:* with a follow-up of 7 years, the International Randomized Study of Interferon and STI571 (IRIS) study showed that 5% patients had discontinued imatinib due to adverse events, 15% due to lack of efficacy and 20% for other reasons. However, 83% of those achieving CCyR maintained the response (Hughes *et al*, 2010). The 6-year event-free survival (EFS), PFS and overall survival (OS) were 83%, 93% and 88% (95% if CML related deaths only included), respectively. A plateau was achieved from the 4th year onwards with an event rate of 0.3–2% (Hochhaus *et al*, 2009). In the IRIS study, patients who achieved MMR by 18 months had 100% freedom from progression to AP/BC and 95% EFS at 7 years with only a 3% probability of loss of CCyR compared with 26% for patients with CCyR but no MMR (Hughes *et al*, 2010). The ELN consensus document (Baccarani *et al*, 2009) and others have demonstrated that increasing the dose of imatinib produced no difference in the molecular response at 12 months, even if the response was quicker at higher doses. A partial cytogenetic response at 12 months (1–35% Ph<sup>+</sup> metaphases) has a significantly poorer PFS (De Lavallade *et al*, 2008).

*Paediatric data:* treatment of childhood CML with imatinib as first line agent in different trials ( $n = 150$ ) has shown that in CP 96% achieve complete haematological response (CHR) and 69% CCyR at 12 months (Suttorp *et al*, 2009a). The French CML IV study ( $n = 44$ ) showed 86% CHR at

3 months and 62% CCyR at 12 months. Thirty-one percent achieved MMR at 12 months and with a median follow-up of 31 months the PFS of this cohort was 98%. However, 20% had discontinued imatinib, mainly because of suboptimal response. The most common side effects were neutropenia and musculoskeletal events (Millot *et al*, 2011).

Imatinib-treated patients show a biphasic molecular response. There is a rapid initial drop in the level of *BCR-ABL1*, reflecting the clearance of mature CML progeny, followed by a second phase with a shallow gradient reflecting the gradual depletion of the less-sensitive CML granulocyte-macrophage precursor pool, which is relatively resistant to imatinib (Roeder *et al*, 2006). Approximately, 40% patients with a stable CMR for at least 2 years are able to stop imatinib and remain in molecular remission for at least 2 years. Molecular relapse occurred in around 60% of the patients after a median interval of 4 months, and relapses after 6 months are uncommon, but can still occur (Mahon *et al*, 2010). Stopping imatinib is not recommended outside a clinical trial. The STOPIMaPED (an international collaborative study to discontinue Imatinib/Glivec® in paediatric CML patients with sustained complete molecular response) study is currently in preparation in order to address the question of discontinuation in the paediatric population (E. de Bont, University Medical Centre Groningen, Groningen, NL).

**Dosage and administration.** Two hundred and sixty to 340 mg/m<sup>2</sup> orally once daily gives drug exposure similar to 400–600 mg adult dosage. It is usual to take it in the morning with breakfast, though some patients prefer it before going to sleep to avoid nausea. Imatinib is a local irritant, therefore it ought to be taken in a sitting position with a large glass of water or apple juice (minimum 100 ml). Tablets may be dispersed in water or apple juice using 50 ml for 100 mg tablet, 200 ml for 400 mg tablet. The contents must be stirred until dissolved and used immediately. For children <3 years of age it is recommended that at least 120 ml of water or food (i.e. yoghurt or apple puree) are taken to avoid oesophageal irritation.

The starting dose is:

- 1 CP: 260–300 mg/m<sup>2</sup> (maximum absolute dose 400 mg)
- 2 AP: 400 mg/m<sup>2</sup> (maximum absolute dose 600 mg)
- 3 BC: 500 mg/m<sup>2</sup> (maximum absolute dose 800 mg)

The dose should be calculated to the nearest 100 mg, which is the size of the smallest tablet and preferably upwards, if tolerated, as active metabolites have a shorter half-life in children than in adults and patients with low plasma levels are less likely to achieve CCyR (Picard *et al*, 2007). Female teenagers must be advised to avoid conception while taking imatinib because of the rate of serious fetal abnormalities is higher than expected (Apperley, 2009b).

If on hydroxycarbamide, this should be stopped once haematological control, not normalization, is achieved. Imatinib and hydroxycarbamide can be used concomitantly, imatinib

should be introduced as soon as the diagnosis of CML has been confirmed.

The WBC count usually starts to fall in 1–2 weeks and normalizes in 6 weeks. Platelet counts usually normalize after 1–3 weeks, but can take 3–6 weeks if the platelet count is >700 × 10<sup>9</sup>/l.

**Management of toxicity.** Imatinib toxicity is common but the effects are generally mild to moderate. Side effects in children occur with the same or less frequency and are less severe than in adults (Bond *et al*, 2008; Mauro & Deininger, 2009). In the largest series (Millot *et al*, 2006) the commonest toxicity was neutropenia and thrombocytopenia; non-haematological toxicity was seen in 50% and was mainly infection, skin rashes, nausea and vomiting.

Myelosuppression occurs in a quarter of CP patients (50% of AP) especially in the first 6 weeks, a rate higher than seen in adults. 27%, 5% and 2.5% developed grade 3 or 4 neutropenia, thrombocytopenia and anaemia, respectively (Millot *et al*, 2011). Management may be difficult and should be discussed with experienced colleagues as reduced doses appear to reduce the chance of CCyR and a change in blood counts may indicate disease progression or drug interaction.

- 1 anaemia: should be managed by transfusion (or erythropoietin) rather than dose reduction.
- 2 neutrophils <1.0 × 10<sup>9</sup>/l: stop for up to 2 weeks; restart when neutrophils >1.0 × 10<sup>9</sup>/l. Consider adding granulocyte colony-stimulating factor (G-CSF) if persistent neutropenia and still in CP. Restart imatinib at full dose if neutropenia <2 weeks, otherwise reduce dose by 20%.
- 3 platelet counts <50 × 10<sup>9</sup>/l: stop; restart when platelets >100 × 10<sup>9</sup>/l. Reduce dose by 20% if recurrent.

Gastro-intestinal (GI) symptoms are common, particularly nausea in the first weeks of treatment. Strategies to overcome this include adding an antiemetic, such as ondansetron, and taking imatinib before going to bed. Imatinib bioavailability is not significantly affected by the administration of food, except grapefruit juice.

Frequent side effects:

- 1 oedema/fluid retention: consider oral diuretic, if severe pleural effusion (rare occurrence) thoracentesis and brief course of steroids
- 2 muscle cramps: supportive, consider calcium/magnesium repletion
- 3 bone pain: affects 10% of children and lessens with longer therapy, manage with non-steroidal anti-inflammatory agents
- 4 skin rash (pruritic/maculopapular): observation and consider topical steroids
- 5 diarrhoea
- 6 lethargy
- 7 weight gain



Less frequent side effects:

- 1 abnormal liver function tests (occasionally severe hepatotoxicity: monitor if concomitant use of paracetamol)

*Drug interactions:* because of the inherent risk of either reduced activity or enhanced toxicity of the concomitant medication and/or imatinib, drugs known to interact with the same CYP450 isoenzymes (2D6 and 3A4) as imatinib should be used with caution (see Appendix II).

*Bone metabolism and longitudinal growth*—There is evidence in animal studies (Vandyke *et al*, 2009), clinical cases (Millot *et al*, 2009; Schmid *et al*, 2009) and prospective studies (Giona *et al*, 2013) that imatinib dysregulates bone remodelling. In adults, imatinib is well known to cause hypocalcaemia and hypophosphataemia, but there is evidence of exhibiting a different effect on bone metabolism than that encountered in children (Fitter *et al*, 2008; Shima *et al*, 2011; Jaeger *et al*, 2012). Children, particularly if treatment is initiated when prepubertal, are at an increased risk of impaired bone remodelling, which may result in growth retardation or arrest (Suttorp & Millot, 2010) with highly significant reduction in height standard deviation scores, possibly due to the alternative targets of imatinib, KIT and PDGFR (Bansal *et al*, 2012). There is also a recent report of acquired growth hormone deficiency as the cause of loss in longitudinal growth as an alternative cause to downstream targets (Hobernicht *et al*, 2011). The optimal approach to children suffering from this side effect remains to be defined. Any decision to stop TKI therapy should only be taken as part of a study.

*Potential cardiotoxicity*—There is potential cardiotoxicity of imatinib due to inhibition of ABL1 in cardiac tissue, which has been shown to have detrimental effects on the viability of cardiomyocytes in animal models, but in large cohorts of adult patients this appears to be very rare (Kerkela *et al*, 2006). Although there is no current evidence that this should influence clinical decision-making, it might be an issue of concern for long-term therapy in children.

*Monitoring.* Routine monitoring for toxicity:

- 1 Full blood count, reticulocytes, urea, electrolytes, creatinine, liver function tests, calcium, phosphate and magnesium:
  - a 1st 4 weeks: weekly
  - b 2nd and 3rd month: every 2 weeks
  - c 4th to 6th month: every 4 weeks
  - d 7th month to 1 year: every 6 weeks
  - e After 1 year: every 3 months
- 2 Height and weight: every 3 months
- 3 Yearly:
  - a Echocardiogram
  - b Vitamin D
  - c Parathyroid hormone

- 4 5-yearly:
  - a DEXA (dual-energy X-ray absorptiometry) scan

Monitoring disease response:

- 1 Bone marrow aspirate/cytogenetics (FISH for *BCR-ABL1* may be used if Giemsa-banding fails): every 3 months until CCyR, then only if loss of response or myelodysplastic changes.
- 2 Quantitative PCR for *BCR-ABL1* on peripheral blood every 3 months

*Milestones and response.* Substantial experience acquired with imatinib has allowed the identification of specific response levels at particular time-points of treatment, representing disease burden and predictive of long-term outcomes. This has been developed by the ELN (Baccarani *et al*, 2009) and has been modified to include more recent findings regarding molecular responses (Table III). *Optimal response* indicates that change in therapy is unlikely to improve survival. In CP with imatinib as first line treatment, this is projected to be close to 100% after 6–7 years. Failure to achieve the specified response level at a specific milestone constitutes a suboptimal response or failure and warrants change of treatment.

The ELN criteria have been independently validated. The rate of combined suboptimal response and failure in newly diagnosed patients is 3.7% at 3 months (25% if *BCR-ABL1* <10% criteria, which was not part of the original criteria used), 12.9% at 6 months, 20.8% at 12 months and 42.1% at 18 months (Marin *et al*, 2008). There are no similar data for children. However, similar responses can be derived from paediatric studies. The German CML-PAED II study ( $n = 61$ , 56 in CP) showed that of those entering the study in CP, 5% (2/42) of patients failed to achieve CHR at 3 months, 7% (2/28) failed CCyR at 12 months and 15% (2/19) had a suboptimal molecular response at 18 months (Suttorp *et al*, 2009a). Overall 15% patients stopped imatinib, 10% because of insufficient response and 5% because of toxicity. Ten percent (5/56) achieved CMR (9–33 months). However, this was an early analysis and follow-up was limited. Data from the French CML-IV paediatric trial for newly diagnosed patients in CP with a median follow-up of 33 months, encountered a substantially higher rate of suboptimal responses with only 86% achieving CHR at 3 months, 61% of patients achieving a CCyR at 12 months, and a rate of MMR of 57% similar (though not necessarily at 18 months) to the findings in adults. Thirty percent patients discontinued imatinib, <5% due to toxicity (Millot *et al*, 2011).

The molecular response at 3 months, used for discriminating long-term outcome for adult patients treated with TKIs, has been identified by two independent groups (Hanfstein *et al*, 2012; Marin *et al*, 2012). *BCR-ABL1* transcript levels >10% identify a high-risk group of patients with a significantly lower OS and PFS.

**Table III.** Modified ELN guideline for optimal treatment response to imatinib in CML (Baccarani *et al*, 2009, 2013).

Time	Optimal response	Suboptimal response	Failure	Warnings
Diagnosis	N/A	N/A	N/A	CCA/Ph <sup>+</sup> *
3 months	CHR <i>BCR-ABL1</i> <10%	No CyR <i>BCR-ABL1</i> >10%	Less than CHR	N/A
6 months	At least PCyR	Less than PCyR	No CyR	N/A
12 months	CCyR	PCyR	Less than PCyR	Less than MMR
18 months	MMR	Less than MMR	Less than CCyR	N/A
Any time	Stable or improving MMR	Loss of MMR Mutations†	Loss of CHR Loss of CCyR, Mutations‡ CCA/Ph <sup>+</sup> *	Increase in transcript levels ≥ 0.05% CCA/Ph <sup>-</sup>

CCA, clonal cytogenetic abnormalities in either Philadelphia positive (CCA/Ph<sup>+</sup>) or negative cells (CCA/Ph<sup>-</sup>), as indicated; CHR, complete haematological response; CyR, cytogenetic response; ELN, European LeukemiaNet; MMR, major molecular response; N/A, not applicable; PCyR, partial cytogenetic response.

\*CCA/Ph<sup>+</sup> (clonal cytogenetic abnormalities in Philadelphia positive cells) 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 clonal cytogenetic abnormalities in at least two Ph<sup>+</sup> cells.

†TKD mutations still sensitive to imatinib.

‡TKD mutations poorly sensitive to imatinib.

Clonal cytogenetic abnormalities in Ph<sup>+</sup> cells (CCA/Ph<sup>+</sup>) is a 'warning' factor at diagnosis. Major route additional cytogenetic abnormalities (second Ph chromosome, trisomy 8, isochromosome 17q or trisomy 19) have a negative impact on survival and PFS (Fabarius *et al*, 2011). The prognosis for patients with clonal cytogenetic abnormalities in Ph negative cells (CCA/Ph<sup>-</sup>) is driven by response to imatinib in the absence of morphological evidence of myelodysplastic syndrome (MDS) and therefore it is a warning sign requiring monitoring with 3 monthly BM aspirates, rather than a criteria to change treatment (Deininger *et al*, 2007).

*Significance of changes in transcript levels:* fluctuation in *BCR-ABL1* transcript levels does not necessarily have a clinical implication and/or anticipate a loss of response to imatinib. Two to fivefold change (up to 0.5-log) is within the variability of the technique (Kantarjian *et al*, 2008). At very low transcript levels, this can be the result of sampling effect. However, a rise >0.05% is almost certainly real. A rising level is associated with a greater risk of a tyrosine kinase domain (TKD) mutation acquisition and resistance (Soverini *et al*, 2005). Confirmation is required in at least an independent sample a month apart and it is better to establish a trend of increase resulting from two consecutive rises. If the rise is >0.05%, but there is no loss of MMR, mutation analysis should be performed. However, a rise in *BCR-ABL1* transcript levels in those who concomitantly lose MMR is a reproducible predictor for loss of CCyR and is a suboptimal response (Kantarjian *et al*, 2009; Marin *et al*, 2009). There is a higher incidence of cytogenetic relapse among patients who never achieved a MMR and had a 10-fold increase of transcript levels (Cortes *et al*, 2005).

*Lack of compliance* is the single most frequent factor for loss of CCyR in long-term imatinib-treated patients (Ibrahim *et al*, 2011) and should be carefully checked at any evaluation, particularly when dealing with patients in adolescence.

Where available, performing imatinib plasma levels and monitoring of imatinib to target a concentration of imatinib above 1000 ng/ml could be the first step if there is a suboptimal response (Cortes *et al*, 2009).

#### *Treatment with second generation TKIs*

Randomized phase 3 studies have recently demonstrated the superiority of both dasatinib and nilotinib in the achievement of both CCyR and MMR (Kantarjian *et al*, 2010, 2012; Saglio *et al*, 2010a). However, it is still not known whether this translates into superior long-term OS and PFS. Importantly, approximately 50% of patients who are intolerant or resistant to imatinib achieve CCyR with 2G TKIs (Shah *et al*, 2010). There are limited data about the use of dasatinib in children; these children should be enrolled in opened trials if possible (i.e. the BMS phase 2 trial CA180-226). In a phase 1 trial all eight evaluable patients had a response, including three CCyR and three partial cytogenetic remissions (PCyR; Aplenc *et al*, 2011). Information on nilotinib is limited, but soon expected to be available from a current phase I trial. Dasatinib is associated with the development of pleural effusions (observed in 30.2% of patients older than 60 years of age) and nilotinib carries a warning regarding QT prolongation and sudden death (Latagliata *et al*, 2012). Pancreatitis has been described with the use of nilotinib.

There has been a phase 3 study of dasatinib in BC of CML (Saglio *et al*, 2010b). In myeloid BC, 25% patients achieved a major CyR (CCyR and PCyR) at a median time of 2.9 months with a median duration of 7.7 months. In lymphoid BC, 50% patients achieved a major cytogenetic remission (MCyR) at a median time of 1.4 months with a median duration of 4 months. The OS rate at 2 years was 24–28% for patients with myeloblast crisis and 16–21% for patients with lymphoid BC. Dasatinib crosses the blood–brain barrier and shows

long lasting responses in Ph<sup>+</sup> central nervous system disease (Porkka *et al*, 2008).

**Dosage and administration.** *Dasatinib:* the dose of dasatinib is 60–80 mg/m<sup>2</sup> per d (routine dose in adults 100 mg once daily). Tablets can be allowed to dissolve over 20 min in 30 ml lemonade, preservative-free apple or orange juice. After ingestion, rinse the residue off the glass with 15 ml of the juice and administer. For patients in CP with suboptimal response or failure to imatinib use 60 mg/m<sup>2</sup> once daily, for patients in AP/BC use 80 mg/m<sup>2</sup> in two divided doses (maximum dose in adults: 140 mg divided in two doses).

*Nilotinib:* the paediatric dosing for nilotinib is yet to be established (phase 1 trial ongoing).

**Milestones and response.** The responses at specific milestones have also been developed by the ELN (Baccarani *et al*, 2009, 2013), but differ from those for imatinib (Table IV).

### BMT

OS ranges from 60% to 80% with better results in matched sibling donors (87%) compared with matched unrelated donors (59%). Despite the role of graft-versus-leukaemia effect, the transplant-related mortality is lower and best results are obtained when graft-versus-host disease (GvHD) grade II–IV does not occur (OS of 91% and 69% for sibling and unrelated donors, respectively Cwynarski *et al*, 2003). No significant differences in OS for both related and unre-

**Table IV.** Modified ELN guidelines for optimal treatment response to 2G TKIs in CML (Baccarani *et al*, 2009, 2013).

Time	Optimal response	Suboptimal response	Failure	Warnings
Baseline	N/A	N/A	N/A	CCA/Ph <sup>+</sup> Mutations
3 months	CHR At least PCyR	Minor CyR	No CyR New mutations	Minimal CyR
6 months	CCyR	PCyR	Minimal CyR New mutations	Minor CyR
12 months	MMR	Less than MMR	Less than PCyR	N/A

CCA, clonal cytogenetic abnormalities in either Philadelphia positive (CCA/Ph<sup>+</sup>) or negative cells (CCA/Ph<sup>-</sup>), as indicated; CHR, complete haematological response; CCyR, complete cytogenetic response; CyR, cytogenetic response; ELN, European LeukemiaNet; MMR, major molecular response; N/A, not applicable; PCyR, partial cytogenetic response; 2G TKI, second generation tyrosine kinase inhibitor. \*CCA/Ph<sup>+</sup> (clonal cytogenetic abnormalities in Philadelphia positive cells) is a 'warning' factor at baseline, 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 clonal cytogenetic abnormalities in at least two Ph<sup>+</sup> cells.

lated transplantation have been found when comparing total body irradiation with busulfan/cyclophosphamide conditioning regimens (Suttorp *et al*, 2009b). MCyR at the time of BMT, as achieved by prior imatinib treatment, predicts an excellent 5-year OS of 81·9%, at least in the unrelated setting (Muramatsu *et al*, 2010).

In the European Group for Blood and Marrow Transplantation study, children transplanted in AP had an OS of 46% and 39%, EFS of 35% and 34%, relapse rate of 49% and 20% and transplant-related mortality of 16% and 46% for sibling and unrelated transplantation, respectively (Cwynarski *et al*, 2003).

### Tyrosine kinase domain mutations

There are >90 different mutation involving different amino acids reported, though only a subset are associated with TKI failure. *BCR-ABL1* kinase domain mutations are not induced but arise independently and are selected by TKIs (Roche-Lestienne *et al*, 2002). They may theoretically pre-exist before the start of therapy and have been reported only in some cases with advanced-phase disease (Willis *et al*, 2005).

### Monitoring

Given that <3% of CP patients develop a mutation (Khorashad *et al*, 2008), routine mutation monitoring of CP patients with optimal response during therapy is not recommended. Therefore TKD mutation analysis is reserved for treatment failure or suboptimal response. Development of a mutation predicts the loss of CCyR. Overall, a third of patients who fail imatinib treatment and 16% with suboptimal response harbour a mutation (Baccarani *et al*, 2006) and this information should direct treatment modification.

Sensitivity of mutation analysis by direct sequencing is 15–25% (Soverini *et al*, 2004), which can be improved if preceded by denaturing high performance liquid chromatography (HPLC) to 1–10% (Deininger *et al*, 2007). The relative sensitivity of different methods is not a limitation because, so far, low level mutations (<20%) have not been proven to be of clinical significance in predicting resistance and disease progression. Mutations found in rare Ph<sup>+</sup> cells are not necessarily selected and able to sustain long-term haemopoiesis (Sherbenou *et al*, 2007; Soverini *et al*, 2011).

Mutation analysis should be performed in the following instances, having first ruled out non-adherence to treatment, particularly in teenagers:

- 1 At diagnosis: AP/BC patients only
- 2 First line imatinib therapy: treatment failure and suboptimal response
- 3 Second line dasatinib or nilotinib therapy: haematological or cytogenetic failure

When selecting a TKI based on the results of *in vitro* sensitivity testing, it must be kept in mind that there are

ongoing controversies with regard to the simple use of tables listing mutations and 50% inhibitory concentration (IC<sub>50</sub>) values. Some experts believe that the latter on its own should not guide physician choices for therapy (Khorashad *et al*, 2006; Redaelli *et al*, 2009; Laneuville *et al*, 2010; Branford & Hughes, 2011). Data from *in vitro* analyses do not account for factors relevant *in vivo*, such as protein binding and activity of cellular influx/efflux pumps or a variety of other factors affecting clinical response to a 2G TKI, and thus generally provide an inadequate predictability of treatment response (Bixby & Talpaz, 2011).

As performing a mutation analysis may require some time, we recommend the following pragmatic approach once imatinib resistance based on rising *BCR-ABL1* transcript levels is suspected:

- 1 rule out non-adherence to treatment (clinical history, determination of serum drug level if available)
- 2 collect blood for mutation analysis, perform bone marrow aspiration for cytogenetic analysis
- 3 switch treatment to a 2G TKI
- 4 4 weeks later, repeat determination of *BCR-ABL1* blood transcripts level
- 5 interpret findings of cytogenetic analysis and mutation analysis in the light of the *BCR-ABL1 in vivo* response rate to the chosen 2G TKI

#### Management of mutations in patients on imatinib

For the most frequent *BCR-ABL1* gene mutations (i.e. M244V, G250E, Y253F/H, E255K/V, T315I, F317L, M351T, E355G, F359V and H396R/P) clinical and laboratory (IC<sub>50</sub>) experience is that imatinib treatment is no longer advised. However, the possibility of constitutional single nucleotide polymorphisms or a bystander effect not contributing to the mechanism of resistance has to be considered for rare or unreported mutations with unknown IC<sub>50</sub> and therapy managed according to response. Imatinib-resistant patients harbouring a TKI mutation have a higher likelihood of developing additional mutations under the selective pressure of the novel TKI: 45% achieved and subsequently lost response with evidence of newly acquired mutations (Soverini *et al*, 2009). Hence, sibling and unrelated BMT is indicated in this situation, but an attempt to achieve major CyR or best possible response with a 2G TKI beforehand should be sought (see algorithm, Section 6).

2G TKIs have a narrow spectrum of mutations retaining insensitivity and is non-overlapping except for *BCR-ABL1* T315I. Best available treatment for patients with no suitable related or unrelated donor is (Soverini *et al*, 2011):

- 1 BMT always or investigational drug: *BCR-ABL1* T315I
- 2 Dasatinib rather than nilotinib: *BCR-ABL1* Y253H, *BCR-ABL1* E255K/V and *BCR-ABL1* F359V/C/I
- 3 Nilotinib rather than dasatinib: *BCR-ABL1* V299L, *BCR-ABL1* T315A and *BCR-ABL1* F317L/V/I/C

#### 4 Dasatinib and nilotinib equally effective: other mutations

### Treatment algorithms according to phase

#### Chronic and accelerated phase

The treatment algorithms according to phase incorporate the evidence presented in previous sections and take into account the specific character of CML treatment in childhood: the need to balance the importance of cure, which at present is only proven for BMT, and the potential for leukaemic stem cell depletion in the long-term with the use of TKIs and novel agents (Figs 1 and 2). As the incidence of CML is greatest in the teenage years, the forthcoming availability of therapeutic agents licensed or approved as part of studies for use in adults needs to be taken into account as the young person grows and may become a candidate to use them.

When a 2G TKI is indicated at present, unless otherwise indicated because of a TKI mutation, dasatinib is the agent of choice. This recommendation reflects the limited experience with dasatinib from a phase II trial and unpublished phase I trial experience with nilotinib.

There are circumstances in the context of CML in childhood and young people when BMT is the most appropriate modality of treatment and hence an acceptable deviation from the algorithms (Fig 2). These comprise:

- 1 lack of compliance despite maximum support
- 2 serious side effects inherent to all TKIs
- 3 patient choice of balancing the risk of BMT *versus* the probability of achieving a definitive cure following appropriate counselling

#### Blast crisis

BC is usually either myeloid (60–80%) or lymphoid (20–30%), but a mixed-lineage phenotype can occur and, rarely, patients may present in BC without a diagnosed preceding CP and discrimination from Ph<sup>+</sup> acute leukaemia may be impossible.

Treatment with a 2G TKI according to TKD mutation and combined with chemotherapy should be given and allo-BMT planned as quickly as possible (Fig 3), preferably within 3 months (Hehlmann, 2012). Most long-term survivors in BC have received an allograft, mostly in second CP (Saussele *et al*, 2010) and obtaining a second CP is the most important prognostic factor for survival (Wadhwa *et al*, 2002). Acute lymphoblastic leukaemia and acute myeloid leukaemia induction according to type of BC are suitable regimens (Hehlmann, 2012). If lymphoid crisis, it requires the addition of six doses of intrathecal chemotherapy. Following BMT, the patient could be restarted on 2G TKI as early day +30 provided there is adequate engraftment, and maintained thereafter for a prolonged period (Klyuchnikov *et al*, 2010). The



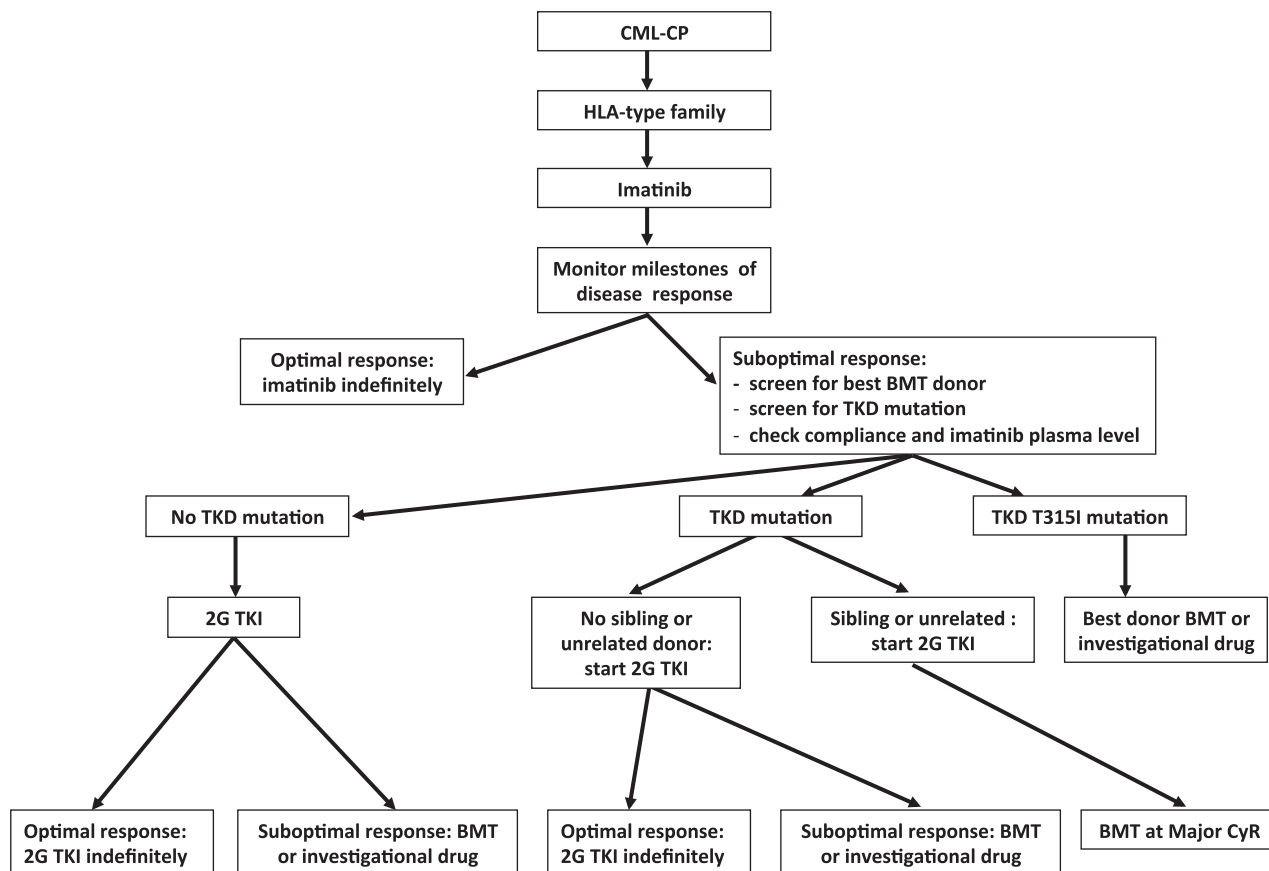


Fig 1. Algorithm for treatment of CML in Chronic Phase. BMT, bone marrow transplantation; CML-CP, chronic myeloid leukaemia in chronic phase; CyR, cytogenetic response; HLA, human leucocyte antigen; TKD, tyrosine kinase domain; T315I mutation, *BCR-ABL1* T315I; 2G TKI, second generation tyrosine kinase inhibitor.

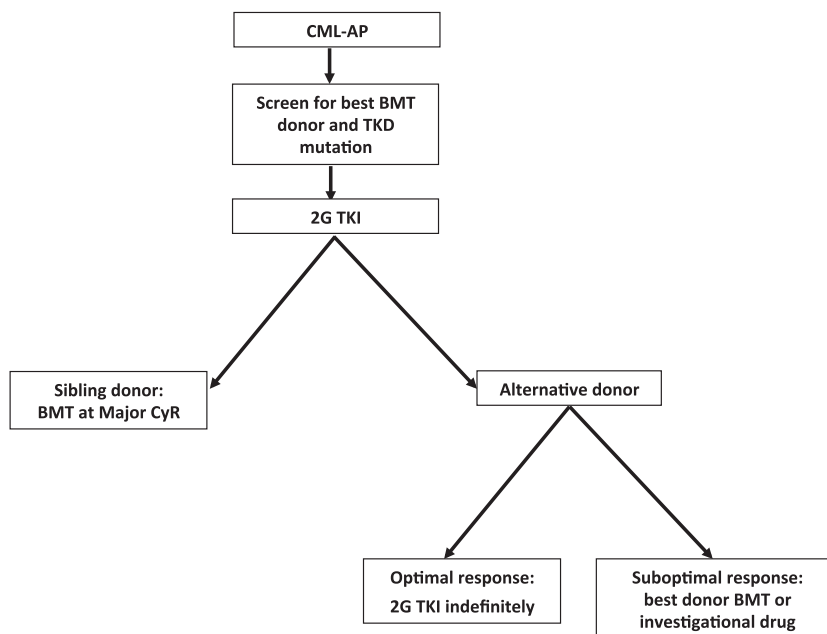


Fig 2. Algorithm for treatment of CML in Accelerated Phase. BMT, bone marrow transplantation; CML-AP, chronic myeloid leukaemia in accelerated phase; CyR, cytogenetic response; HLA, human leucocyte antigen; TKD, tyrosine kinase domain; 2G TKI, second generation tyrosine kinase inhibitor.

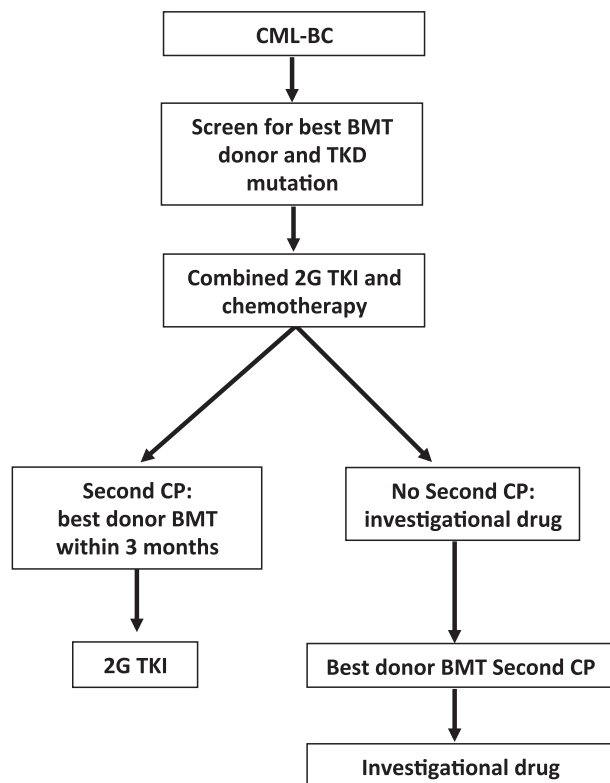


Fig 3. Algorithm for treatment of CML in Blast Crisis. BMT, bone marrow transplantation; CML-BC, chronic myeloid leukaemia in blast crisis; CP, chronic phase; TKD, tyrosine kinase domain; 2G TKI, second generation tyrosine kinase inhibitor.

*BCR-ABL1/ABL1* ratio should be monitored 3 monthly until undetectable, then 6-monthly (Hehlmann, 2012).

## Compliance

The half-life of imatinib is in the region of 18 h, thus lack of compliance for just 1 week would completely eliminate the drug from plasma (Cortes *et al*, 2009). Therefore, non-adherence to TKI treatment is a potential cause of treatment failure or suboptimal response, of particular relevance for our patient population as the incidence of CML is most frequent in adolescence. In fact, even in adult patients it has been established as the single most frequent factor for suboptimal responses, loss of CCyR in long-term imatinib-treated patients and achieving molecular responses (Noens *et al*, 2009; Marin *et al*, 2010; Ibrahim *et al*, 2011). Before making any treatment decisions compliance should be thoroughly investigated as part of the

clinical history and, where available, performing imatinib plasma levels. Imatinib should be targeted to a concentration above 1000 ng/ml and this could be the first step if there is a suboptimal response (Cortes *et al*, 2009).

## Imatinib and pregnancy

Animal data suggest that imatinib at standard dosages is unlikely to impair fertility in either adult males or females, but human data remains limited (Schultheis *et al*, 2012). Children born to men who are actively taking imatinib at the time of conception appear healthy and current advice is not to discontinue treatment. In contrast, the data relating to children born to women exposed to imatinib during pregnancy are less encouraging (Apperley, 2009a,b). In one study, 50% (63 of 125) of women treated with imatinib gave birth to healthy babies (Pye *et al*, 2008). However, 12 infants exposed to imatinib during the first trimester had congenital abnormalities, especially of the kidneys, skeleton, heart, brain and gut (i.e. exomphalos). For female patients with a prolonged MMR, substitution of TKI with IFN- $\alpha$  is recommended (Ali *et al*, 2004; Burchert *et al*, 2010) and for patients with an inferior response, pregnancy should be postponed or to the TKI should be substituted with IFN- $\alpha$  during the first trimester and TKI readministered in the second or third trimester (Brenner *et al*, 2012). The effect of imatinib cessation on disease course is still under study, but most studies report disease relapse after imatinib discontinuation, with only a fraction of patients achieving complete remission after readministration of imatinib (Ault *et al*, 2006). However, for those patients with durable CMR (at least 2 years) a more favourable situation exists, with studies demonstrating disease control following reintroduction of TKI (Mahon *et al*, 2010). At present the data on 2G TKIs is too limited to make specific recommendations, but they also seem teratogenic (Cortes *et al*, 2008).

## Author contributions

JDLF wrote the manuscript, AB, AB, EDB, MFD, MS and FM reviewed the manuscript.

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## References

- Ali, R., Ozkalemkas, F., Ozkocaman, V., Ozcelik, T., Ozan, U., Kimya, Y. & Tunali, A. (2004) Successful pregnancy and delivery in a patient with chronic myelogenous leukemia (CML), and management of CML with leukapheresis during pregnancy: a case report and review of the literature. *Japanese Journal of Clinical Oncology*, **34**, 215–217.
- Andolina, J.R., Neudorf, S.M. & Corey, S.J. (2012) How I treat childhood CML. *Blood*, **119**, 1821–1830.
- Aplenc, R., Blaney, S.M., Strauss, L.C., Balis, F.M., Shusterman, S., Ingle, A.M., Agrawal, S., Sun, J., Wright, J.J. & Adamson, P.C. (2011) Pediatric phase I trial and pharmacokinetic study of dasatinib: a report from the children's oncology group phase I consortium. *Journal of Clinical Oncology*, **29**, 839–844.
- Apperley, J. (2009a) Issues of imatinib and pregnancy outcome. *Journal of the National Comprehensive Cancer Network*, **7**, 1050–1058.

- Apperley, J. (2009b) CML in pregnancy and childhood. *Best Practice & Research Clinical Haematology*, **22**, 455–474.
- Ault, P., Kantarjian, H., O'Brien, S., Faderl, S., Beran, M., Rios, M.B., Koller, C., Giles, F., Keating, M., Talpaz, M. & Cortes, J. (2006) Pregnancy among patients with chronic myeloid leukemia treated with imatinib. *Journal of Clinical Oncology*, **24**, 1204–1208.
- Baccarani, M., Saglio, G., Goldman, J., Hochhaus, A., Simonsson, B., Appelbaum, F., Apperley, J., Cervantes, F., Cortes, J., Deininger, M., Gratwohl, A., Guilhot, F., Horowitz, M., Hughes, T., Kantarjian, H., Larson, R., Niederwieser, D., Silver, R. & Hehlmann, R. (2006) Evolving concepts in the management of chronic myeloid leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. *Blood*, **108**, 1809–1820.
- 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, R.T., Goldman, J. & Hehlmann, R. (2009) Chronic myeloid leukemia: an update of concepts and management recommendations of European LeukemiaNet. *Journal of Clinical Oncology*, **27**, 6041–6051.
- Baccarani, M., Deininger, M.W., Rosti, G., Hochhaus, A., Soverini, S., Apperley, J.F., Cervantes, F., Clark, R.E., Cortes, J.E., Guilhot, F., Hjorth-Hansen, H., Hughes, T.P., Kantarjian, H.M., Kim, D.W., Larson, R.A., Lipton, J.H., Mahon, F.X., Martinelli, G., Mayer, J., Muller, M.C., Niederwieser, D., Pane, F., Radich, J.P., Rousselot, P., Saglio, G., Saussele, S., Schiffer, C., Silver, R., Simonsson, B., Stegmann, J.L., Goldman, J.M. & Hehlmann, R. (2013) European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. *Blood*, **122**, 872–884.
- Bansal, D., Shava, U., Varma, N., Trehan, A. & Marwaha, R.K. (2012) Imatinib has adverse effect on growth in children with chronic myeloid leukemia. *Pediatric Blood & Cancer*, **59**, 481–484.
- Bashir, Q., de Lima, M.J., McMannis, J.D., Garcia-Manero, G., Shpall, E., Kantarjian, H., Cortes, J.E., O'Brien, S.M., Jones, D., Qazilbash, M., Wei, W., Giralt, S.A., Champlin, R.E. & Hosing, C. (2010) Hematopoietic progenitor cell collection in patients with chronic myelogenous leukemia in complete cytogenetic remission after imatinib mesylate therapy. *Leukemia & Lymphoma*, **51**, 1478–1484.
- Bixby, D. & Talpaz, M. (2011) Seeking the causes and solutions to imatinib-resistance in chronic myeloid leukemia. *Leukemia*, **25**, 7–22.
- Bond, M., Bernstein, M.L., Pappo, A., Schultz, K.R., Krailo, M., Blaney, S.M. & Adamson, P.C. (2008) A phase II study of imatinib mesylate in children with refractory or relapsed solid tumors: a Children's Oncology Group study. *Pediatric Blood & Cancer*, **50**, 254–258.
- Branford, S. & Hughes, T.P. (2011) Mutational analysis in chronic myeloid leukemia: when and what to do? *Current Opinion in Hematology*, **18**, 111–116.
- Brenner, B., Avivi, I. & Lishner, M. (2012) Haematological cancers in pregnancy. *Lancet*, **379**, 580–587.
- Burchert, A., Muller, M.C., Kostrewa, P., Erben, P., Bostel, T., Liebler, S., Hehlmann, R., Neubauer, A. & Hochhaus, A. (2010) Sustained molecular response with interferon alfa maintenance after induction therapy with imatinib plus interferon alfa in patients with chronic myeloid leukemia. *Journal of Clinical Oncology*, **28**, 1429–1435.
- Cawein, M., Lappat, E.J. & Rackley, J.W. (1965) Down's syndrome and chronic myelogenous leukemia. *Archives of Internal Medicine*, **116**, 505–508.
- Champagne, M.A., Capdeville, R., Krailo, M., Qu, W., Peng, B., Rosamilia, M., Therrien, M., Zoellner, U., Blaney, S.M. & Bernstein, M. (2004) Imatinib mesylate (STI571) for treatment of children with Philadelphia chromosome-positive leukemia: results from a Children's Oncology Group phase 1 study. *Blood*, **104**, 2655–2660.
- Cortes, J., Talpaz, M., O'Brien, S., Jones, D., Luthra, R., Shan, J., Giles, F., Faderl, S., Vershovsek, S., Garcia-Manero, G., Rios, M.B. & Kantarjian, H. (2005) Molecular responses in patients with chronic myeloid leukemia in chronic phase treated with imatinib mesylate. *Clinical Cancer Research*, **11**, 3425–3432.
- Cortes, J., O'Brien, S., Ault, P., Borthakur, G., Jabbour, E., Bradley-Garelik, B., Debreczeni, K., Yang, D., Liu, D. & Kantarjian, H. (2008) Pregnancy outcomes among patients with chronic myeloid leukemia treated with dasatinib. (Abstract). *Blood*, **112**, 1109.
- Cortes, J.E., Egorin, M.J., Guilhot, F., Molimard, M. & Mahon, F.X. (2009) Pharmacokinetic/pharmacodynamic correlation and blood-level testing in imatinib therapy for chronic myeloid leukemia. *Leukemia*, **23**, 1537–1544.
- Cross, N.C., White, H.E., Muller, M.C., Saglio, G. & Hochhaus, A. (2012) Standardized definitions of molecular response in chronic myeloid leukemia. *Leukemia*, **26**, 2172–2175.
- Cwynarski, K., Roberts, I.A., Iacobelli, S., van Biezen, A., Brand, R., Devergie, A., Vossen, J.M., Aljurf, M., Arcese, W., Locatelli, F., Dini, G., Niethammer, D., Niederwieser, D. & Apperley, J.F. (2003) Stem cell transplantation for chronic myeloid leukemia in children. *Blood*, **102**, 1224–1231.
- De Lavallade, H., Apperley, J.F., Khorashad, J.S., Milojkovic, D., Reid, A.G., Bua, M., Szydlo, R., Olavarria, E., Kaeda, J., Goldman, J.M. & Marin, D. (2008) Imatinib for newly diagnosed patients with chronic myeloid leukemia: incidence of sustained responses in an intention-to-treat analysis. *Journal of Clinical Oncology*, **26**, 3358–3363.
- Deininger, M.W., Cortes, J., Paquette, R., Park, B., Hochhaus, A., Baccarani, M., Stone, R., Fischer, T., Kantarjian, H., Niederwieser, D., Gambacorti-Passerini, C., So, C., Gathmann, I., Goldman, J.M., Smith, D., Druker, B.J. & Guilhot, F. (2007) The prognosis for patients with chronic myeloid leukemia who have clonal cytogenetic abnormalities in Philadelphia chromosome-negative cells. *Cancer*, **110**, 1509–1519.
- Druker, B.J., Guilhot, F., O'Brien, S.G., Gathmann, I., Kantarjian, H., Gattermann, N., Deininger, M.W., Silver, R.T., Goldman, J.M., Stone, R.M., Cervantes, F., Hochhaus, A., Powell, B.L., Gabrielove, J.L., Rousselot, P., Reiffers, J., Cornelissen, J.J., Hughes, T., Agis, H., Fischer, T., Verhoef, G., Shepherd, J., Saglio, G., Gratwohl, A., Nielsen, J.L., Radich, J.P., Simonsson, B., Taylor, K., Baccarani, M., So, C., Letvak, L. & Larson, R.A. (2006) Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. *New England Journal of Medicine*, **355**, 2408–2417.
- Fabarius, A., Leitner, A., Hochhaus, A., Muller, M.C., Hanfstein, B., Haferlach, C., Gohring, G., Schlegelberger, B., Jotterand, M., Reiter, A., Jung-Munkwitz, S., Proetel, U., Schwaab, J., Hofmann, W.K., Schubert, J., Einsele, H., Ho, A.D., Falge, C., Kanz, L., Neubauer, A., Kneba, M., Stegelmann, F., Pfreundschuh, M., Waller, C.F., Spiekermann, K., Baerlocher, G.M., Lauseker, M., Pfirrmann, M., Hasford, J., Saussele, S. & Hehlmann, R. (2011) Impact of additional cytogenetic aberrations at diagnosis on prognosis of CML: long-term observation of 1151 patients from the randomized CML Study IV. *Blood*, **118**, 6760–6768.
- Fitter, S., Dewar, A.L., Kostakis, P., To, L.B., Hughes, T.P., Roberts, M.M., Lynch, K., Vernon-Roberts, B. & Zannettino, A.C. (2008) Long-term imatinib therapy promotes bone formation in CML patients. *Blood*, **111**, 2538–2547.
- Giona, F., Mariani, S., Gnessi, L., Moleti, M.L., Rea, M., De, V.A., Marzella, D., Testi, A.M. & Foa, R. (2013) Bone metabolism, growth rate and pubertal development in children with chronic myeloid leukemia treated with imatinib during puberty. *Haematologica*, **98**, e25–e27.
- Hanfstein, B., Muller, M.C., Hehlmann, R., Erben, P., Lauseker, M., Fabarius, A., Schnitger, S., Haferlach, C., Gohring, G., Proetel, U., Kolb, H.J., Krause, S.W., Hofmann, W.K., Schubert, J., Einsele, H., Dengler, J., Hanel, M., Falge, C., Kanz, L., Neubauer, A., Kneba, M., Stegelmann, F., Pfreundschuh, M., Waller, C.F., Branford, S., Hughes, T.P., Spiekermann, K., Baerlocher, G.M., Pfirrmann, M., Hasford, J., Saussele, S. & Hochhaus, A. (2012) Early molecular and cytogenetic response is predictive for long-term progression-free and overall survival in chronic myeloid leukemia (CML). *Leukemia*, **26**, 2096–2102.
- Hehlmann, R. (2012) How I treat CML blast crisis. *Blood*, **120**, 737–747.
- Hehlmann, R., Heimpel, H., Hasford, J., Kolb, H.J., Pralle, H., Hossfeld, D.K., Queisser, W., Löffler, H., Hochhaus, A. & Heinze, B. (1994) Randomized comparison of interferon-alpha with busulfan and hydroxyurea in chronic myelogenous leukemia. The German CML Study Group. *Blood*, **84**, 4064–4077.

- Hehlmann, R., Lauseker, M., Jung-Munkwitz, S., Leitner, A., Muller, M.C., Pletsch, N., Proetel, U., Haferlach, C., Schlegelberger, B., Balleisen, L., Hanel, M., Pfirrmann, M., Krause, S.W., Nerl, C., Pralle, H., Gratwohl, A., Hossfeld, D.K., Hasford, J., Hochhaus, A. & Saussele, S. (2011) Tolerability-adapted imatinib 800 mg/d versus 400 mg/d versus 400 mg/d plus interferon-alpha in newly diagnosed chronic myeloid leukemia. *Journal of Clinical Oncology*, **29**, 1634–1642.
- Hobernicht, S.L., Schweiger, B., Zeitler, P., Wang, M. & Hunger, S.P. (2011) Acquired growth hormone deficiency in a girl with chronic myelogenous leukemia treated with tyrosine kinase inhibitor therapy. *Pediatric Blood & Cancer*, **56**, 671–673.
- Hochhaus, A., O'Brien, S.G., Guilhot, F., Druker, B.J., Branford, S., Foroni, L., Goldman, J.M., Muller, M.C., Radich, J.P., Rudoltz, M., Mone, M., Gathmann, I., Hughes, T.P. & Larson, R.A. (2009) Six-year follow-up of patients receiving imatinib for the first-line treatment of chronic myeloid leukemia. *Leukemia*, **23**, 1054–1061.
- Hughes, T., Deininger, M., Hochhaus, A., Branford, S., Radich, J., Kaeda, J., Baccarani, M., Cortes, J., Cross, N.C., Druker, B.J., Gabert, J., Grimwade, D., Hehlmann, R., Kamel-Reid, S., Lipton, J.H., Longtine, J., Martinelli, G., Saglio, G., Soverini, S., Stock, W. & Goldman, J.M. (2006) Monitoring CML patients responding to treatment with tyrosine kinase inhibitors: review and recommendations for harmonizing current methodology for detecting BCR-ABL transcripts and kinase domain mutations and for expressing results. *Blood*, **108**, 28–37.
- Hughes, T.P., Hochhaus, A., Branford, S., Muller, M.C., Kaeda, J.S., Foroni, L., Druker, B.J., Guilhot, F., Larson, R.A., O'Brien, S.G., Rudoltz, M.S., Mone, M., Wehrle, E., Modur, V., Goldman, J.M. & Radich, J.P. (2010) Long-term prognostic significance of early molecular response to imatinib in newly diagnosed chronic myeloid leukemia: an analysis from the International Randomized Study of Interferon and STI571 (IRIS). *Blood*, **116**, 3758–3765.
- Ibrahim, A.R., Eliasson, L., Apperley, J.F., Milojkovic, D., Bua, M., Szydlo, R., Mahon, F.X., Kozlowski, K., Paliompeis, C., Foroni, L., Khorashad, J.S., Bazeos, A., Molimard, M., Reid, A., Rezvani, K., Gerrard, G., Goldman, J. & Marin, D. (2011) Poor adherence is the main reason for loss of CCyR and imatinib failure for chronic myeloid leukemia patients on long-term therapy. *Blood*, **117**, 3733–3736.
- Jaeger, B.A., Tauer, J.T., Ulmer, A., Kuhlisch, E., Roth, H.J. & Suttorp, M. (2012) Changes in bone metabolic parameters in children with chronic myeloid leukemia on imatinib treatment. *Medical Science Monitor*, **18**, CR721–CR728.
- Kantarjian, H., Schiffer, C., Jones, D. & Cortes, J. (2008) Monitoring the response and course of chronic myeloid leukemia in the modern era of BCR-ABL tyrosine kinase inhibitors: practical advice on the use and interpretation of monitoring methods. *Blood*, **111**, 1774–1780.
- Kantarjian, H.M., Shan, J., Jones, D., O'Brien, S., Rios, M.B., Jabbour, E. & Cortes, J. (2009) Significance of increasing levels of minimal residual disease in patients with Philadelphia chromosome-positive chronic myelogenous leukemia in complete cytogenetic response. *Journal of Clinical Oncology*, **27**, 3659–3663.
- Kantarjian, H., Shah, N.P., Hochhaus, A., Cortes, J., Shah, S., Ayala, M., Moiraghi, B., Shen, Z., Mayer, J., Pasquini, R., Nakamae, H., Huguet, F., Boque, C., Chuah, C., Bleickardt, E., Bradley-Garelik, M.B., Zhu, C., Sztatowski, T., Shapiro, D. & Baccarani, M. (2010) Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. *New England Journal of Medicine*, **362**, 2260–2270.
- Kantarjian, H.M., Shah, N.P., Cortes, J.E., Baccarani, M., Agarwal, M.B., Undurraga, M.S., Wang, J., Ipina, J.J., Kim, D.W., Ogura, M., Pavlovsky, C., Junghanss, C., Milone, J.H., Nicolini, F.E., Robak, T., Van, D.J., Vellenga, E., Bradley-Garelik, M.B., Zhu, C. & Hochhaus, A. (2012) Dasatinib or imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: 2-year follow-up from a randomized phase 3 trial (DASISION). *Blood*, **119**, 1123–1129.
- Kerkela, R., Grazette, L., Yacobi, R., Iliescu, C., Patten, R., Beahm, C., Walters, B., Shevtsov, S., Pesant, S., Clubb, F.J., Rosenzweig, A., Salomon, R.N., Van Etten, R.A., Alroy, J., Durand, J.B. & Force, T. (2006) Cardiotoxicity of the cancer therapeutic agent imatinib mesylate. *Nature Medicine*, **12**, 908–916.
- Khorashad, J.S., Anand, M., Marin, D., Saunders, S., Al-Jabary, T., Iqbal, A., Margerison, S., Melo, J.V., Goldman, J.M., Apperley, J.F. & Kaeda, J. (2006) The presence of a BCR-ABL mutant allele in CML does not always explain clinical resistance to imatinib. *Leukemia*, **20**, 658–663.
- Khorashad, J.S., de Lavallade, H., Apperley, J.F., Milojkovic, D., Reid, A.G., Bua, M., Szydlo, R., Olavarria, E., Kaeda, J., Goldman, J.M. & Marin, D. (2008) Finding of kinase domain mutations in patients with chronic phase chronic myeloid leukemia responding to imatinib may identify those at high risk of disease progression. *Journal of Clinical Oncology*, **26**, 4806–4813.
- Klyuchnikov, E., Kroger, N., Brummendorf, T.H., Wiedemann, B., Zander, A.R. & Bacher, U. (2010) Current status and perspectives of tyrosine kinase inhibitor treatment in the posttransplant period in patients with chronic myelogenous leukemia (CML). *Biology of Blood & Marrow Transplantation*, **16**, 301–310.
- Kosenow, W. & Pfeiffer, R.A. (1969) Chronic myeloid leukemia in monozygotic twins. *Deutsche Medizinische Wochenschrift*, **94**, 1170.
- Krumbholz, M., Karl, M., Tauer, J.T., Thiede, C., Rascher, W., Suttorp, M. & Metzler, M. (2012) Genomic BCR-ABL1 breakpoints in pediatric chronic myeloid leukemia. *Genes Chromosomes & Cancer*, **51**, 1045–1053.
- Laneville, P., Dilea, C., Yin, O.Q., Woodman, R.C., Mestan, J. & Manley, P.W. (2010) Comparative in vitro cellular data alone are insufficient to predict clinical responses and guide the choice of BCR-ABL inhibitor for treating imatinib-resistant chronic myeloid leukemia. *Journal of Clinical Oncology*, **28**, e169–e171.
- Latagliata, R., Breccia, M., Fava, C., Stagno, F., Tiribelli, M., Luciano, L., Gozzini, A., Gugliotta, G., Annunziata, M., Cavazzini, F., Ferrero, D., Musto, P., Capodanno, I., Iurlo, A., Visani, G., Crugnola, M., Calistri, E., Castagnetti, F., Vigneri, P. & Alimena, G. (2012) Incidence, risk factors and management of pleural effusions during dasatinib treatment in unselected elderly patients with chronic myelogenous leukaemia. *Hematological Oncology*, **31**, 363–369.
- Lee, S.J., Kukreja, M., Wang, T., Giral, S.A., Szer, J., Arora, M., Woolfrey, A.E., Cervantes, F., Champlin, R.E., Gale, R.P., Halter, J., Keating, A., Marks, D.I., McCarthy, P.L., Olavarria, E., Stadtmauer, E.A., Abecasis, M., Gupta, V., Khoury, H.J., George, B., Hale, G.A., Liesveld, J.L., Rizzieri, D.A., Antin, J.H., Bolwell, B.J., Carabasi, M.H., Copelan, E., Ilhan, O., Litzow, M.R., Schouten, H.C., Zander, A.R., Horowitz, M.M. & Maziarz, R.T. (2008) Impact of prior imatinib mesylate on the outcome of hematopoietic cell transplantation for chronic myeloid leukemia. *Blood*, **112**, 3500–3507.
- Mahon, F.X., Rea, D., Guilhot, J., Guilhot, F., Huguet, F., Nicolini, F., Legros, L., Charbonnier, A., Guerci, A., Varet, B., Etienne, G., Reiffers, J. & Rousselot, P. (2010) Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial. *Lancet Oncology*, **11**, 1029–1035.
- Marin, D., Milojkovic, D., Olavarria, E., Khorashad, J.S., de Lavallade, H., Reid, A.G., Foroni, L., Rezvani, K., Bua, M., Dazzi, F., Pavlu, J., Klammer, M., Kaeda, J.S., Goldman, J.M. & Apperley, J.F. (2008) European LeukemiaNet criteria for failure or suboptimal response reliably identify patients with CML in early chronic phase treated with imatinib whose eventual outcome is poor. *Blood*, **112**, 4437–4444.
- Marin, D., Khorashad, J.S., Foroni, L., Milojkovic, D., Szydlo, R., Reid, A.G., Rezvani, K., Bua, M., Goldman, J.M. & Apperley, J.F. (2009) Does a rise in the BCR-ABL1 transcript level identify chronic phase CML patients responding to imatinib who have a high risk of cytogenetic relapse? *British Journal of Haematology*, **145**, 373–375.
- Marin, D., Bazeos, A., Mahon, F.X., Eliasson, L., Milojkovic, D., Bua, M., Apperley, J.F., Szydlo, R., Desai, R., Kozlowski, K., Paliompeis, C., Latham, V., Foroni, L., Molimard, M., Reid, A., Rezvani, K., de Lavallade, H., Guallar, C., Goldman, J. & Khorashad, J.S. (2010) Adherence is the critical factor for achieving molecular responses in patients with chronic myeloid leukemia who achieve complete cytogenetic



- responses on imatinib. *Journal of Clinical Oncology*, **28**, 2381–2388.
- Marin, D., Ibrahim, A.R., Lucas, C., Gerrard, G., Wang, L., Szydlo, R.M., Clark, R.E., Apperley, J.F., Milojkovic, D., Bua, M., Pavlu, J., Paliompeis, C., Reid, A., Rezvani, K., Goldman, J.M. & Foroni, L. (2012) Assessment of BCR-ABL1 transcript levels at 3 months is the only requirement for predicting outcome for patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors. *Journal of Clinical Oncology*, **30**, 232–238.
- Mauro, M.J. & Deininger, M.W. (2009) Management of drug toxicities in chronic myeloid leukaemia. *Best Practice & Research Clinical Haematology*, **22**, 409–429.
- Millot, F., Traore, P., Guilhot, J., Nelken, B., Leblanc, T., Leverger, G., Plantaz, D., Bertrand, Y., Bordigoni, P. & Guilhot, F. (2005) Clinical and biological features at diagnosis in 40 children with chronic myeloid leukemia. *Pediatrics*, **116**, 140–143.
- Millot, F., Guilhot, J., Nelken, B., Leblanc, T., De Bont, E., Becassy, A., Gardner, H., Sufliarska, S., Stary, J., Gschaimeier, H., Guilhot, F. & Suttrop, M. (2006) Imatinib mesylate is effective in children with chronic myelogenous leukemia in late chronic and advanced phase and in relapse after stem cell transplantation. *Leukemia*, **20**, 187–192.
- Millot, F., Baruchel, A., Guilhot, J., Petit, A., Leblanc, T., Bertrand, Y., Mazingue, F., Lutz, P., V erit e, C., Berthou, C., Galambrun, C., Bernard, F., Yacouben, K., Bordigoni, P., Edan, C., Reguerre, Y., Couillaud, G., Cayuela, J.M. & Guilhot, F. (2009) Imatinib is efficient but has a negative impact on growth in children with previously untreated chronic myelogenous leukaemia (CML) in early chronic phase (CP): results of the French national phase IV trial. (Abstract). *Blood*, **114**, 863.
- Millot, F., Baruchel, A., Guilhot, J., Petit, A., Leblanc, T., Bertrand, Y., Mazingue, F., Lutz, P., Verite, C., Berthou, C., Galambrun, C., Bernard, F., Yacouben, K., Bordigoni, P., Edan, C., Reguerre, Y., Couillaud, G., Mechinaud, F., Cayuela, J.M. & Guilhot, F. (2011) Imatinib is effective in children with previously untreated chronic myelogenous leukemia in early chronic phase: results of the French national phase IV trial. *Journal of Clinical Oncology*, **29**, 2827–2832.
- Muramatsu, H., Kojima, S., Yoshimi, A., Atsuta, Y., Kato, K., Nagatoshi, Y., Inoue, M., Koike, K., Kawase, T., Ito, M., Kurosawa, H., Tanizawa, A., Tono, C., Hamamoto, K., Hotta, N., Watanabe, A., Morishima, Y., Kawa, K. & Shimada, H. (2010) Outcome of 125 children with chronic myelogenous leukemia who received transplants from unrelated donors: the Japan Marrow Donor Program. *Biology of Blood & Marrow Transplantation*, **16**, 231–238.
- Noens, L., van Lierde, M.A., De, B.R., Verhoef, G., Zachee, P., Berneman, Z., Martiat, P., Mineur, P., Van, E.K., MacDonald, K., De, G.S., Albrecht, T. & Abraham, I. (2009) Prevalence, determinants, and outcomes of nonadherence to imatinib therapy in patients with chronic myeloid leukemia: the ADAGIO study. *Blood*, **113**, 5401–5411.
- Nurmio, M., Toppari, J., Zaman, F., Andersson, A.M., Paranko, J., Soder, O. & Jahnukainen, K. (2007) Inhibition of tyrosine kinases PDGFR and C-Kit by imatinib mesylate interferes with postnatal testicular development in the rat. *International Journal of Andrology*, **30**, 366–376.
- Ozer, H., George, S.L., Schiffer, C.A., Rao, K., Rao, P.N., Wurster-Hill, D.H., Arthur, D.D., Powell, B., Gottlieb, A., Peterson, B.A., Rai, K., Testa, J.R., LeBeau, M., Tantravahi, R. & Bloomfield, C.D. (1993) Prolonged subcutaneous administration of recombinant alpha 2b interferon in patients with previously untreated Philadelphia chromosome-positive chronic-phase chronic myelogenous leukemia: effect on remission duration and survival: Cancer and Leukemia Group B study 8583. *Blood*, **82**, 2975–2984.
- Picard, S., Titier, K., Etienne, G., Teilhet, E., Ducint, D., Bernard, M.A., Lassalle, R., Marit, G., Reiffers, J., Begaud, B., Moore, N., Molimard, M. & Mahon, F.X. (2007) Trough imatinib plasma levels are associated with both cytogenetic and molecular responses to standard-dose imatinib in chronic myeloid leukemia. *Blood*, **109**, 3496–3499.
- Porkka, K., Koskenvesa, P., Lundan, T., Rimpilainen, J., Mustjoki, S., Smykla, R., Wild, R., Luo, R., Arnan, M., Brethon, B., Eccersley, L., Hjorth-Hansen, H., Hoglund, M., Klamova, H., Knutsen, H., Parikh, S., Raffoux, E., Gruber, F., Brito-Babapulle, F., Dombret, H., Duarte, R.F., Elonen, E., Paquette, R., Zwaan, C.M. & Lee, F.Y. (2008) Dasatinib crosses the blood–brain barrier and is an efficient therapy for central nervous system Philadelphia chromosome-positive leukemia. *Blood*, **112**, 1005–1012.
- Pye, S.M., Cortes, J., Ault, P., Hatfield, A., Kantarjian, H., Pilot, R., Rosti, G. & Apperley, J.F. (2008) The effects of imatinib on pregnancy outcome. *Blood*, **111**, 5505–5508.
- Redaelli, S., Piazza, R., Rostagno, R., Magistroni, V., Perini, P., Marega, M., Gambacorti-Passerini, C. & Boschelli, F. (2009) Activity of bosutinib, dasatinib, and nilotinib against 18 imatinib-resistant BCR/ABL mutants. *Journal of Clinical Oncology*, **27**, 469–471.
- Roche-Lestienne, C., Soenen-Cornu, V., Grardel-Duflos, N., Lai, J.L., Philippe, N., Facon, T., Fenaux, P. & Preudhomme, C. (2002) Several types of mutations of the Abl gene can be found in chronic myeloid leukemia patients resistant to ST1571, and they can pre-exist to the onset of treatment. *Blood*, **100**, 1014–1018.
- Roeder, I., Horn, M., Glauche, I., Hochhaus, A., Mueller, M.C. & Loeffler, M. (2006) Dynamic modeling of imatinib-treated chronic myeloid leukemia: functional insights and clinical implications. *Nature Medicine*, **12**, 1181–1184.
- Saglio, G., Kim, D.W., Issaragrisil, S., Le, C.P., Etienne, G., Lobo, C., Pasquini, R., Clark, R.E., Hochhaus, A., Hughes, T.P., Gallagher, N., Hoenekopp, A., Dong, M., Haque, A., Larson, R.A. & Kantarjian, H.M. (2010a) Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. *New England Journal of Medicine*, **362**, 2251–2259.
- Saglio, G., Hochhaus, A., Goh, Y.T., Masszi, T., Pasquini, R., Maloisel, F., Erben, P., Cortes, J., Paquette, R., Bradley-Garelik, M.B., Zhu, C. & Dombret, H. (2010b) Dasatinib in imatinib-resistant or imatinib-intolerant chronic myeloid leukemia in blast phase after 2 years of follow-up in a phase 3 study: efficacy and tolerability of 140 milligrams once daily and 70 milligrams twice daily. *Cancer*, **116**, 3852–3861.
- Sanz, L., Cervantes, F., Esteve, J., Vilardell, J., Marin, P., Rozman, C. & Montserrat, E. (1996) Chronic myeloid leukemia after renal transplantation: report of a new case and review of the bibliography. *Sangre (Barc)*, **41**, 391–393.
- Saussele, S., Lauseker, M., Gratwohl, A., Beelen, D.W., Bunjes, D., Schwerdtfeger, R., Kolb, H.J., Ho, A.D., Falge, C., Holler, E., Schlimok, G., Zander, A.R., Arnold, R., Kanz, L., Dengler, R., Haferlach, C., Schlegelberger, B., Pfirrmann, M., Muller, M.C., Schnittger, S., Leitner, A., Pletsch, N., Hochhaus, A., Hasford, J. & Hehlmann, R. (2010) Allogeneic hematopoietic stem cell transplantation (allo SCT) for chronic myeloid leukemia in the imatinib era: evaluation of its impact within a subgroup of the randomized German CML Study IV. *Blood*, **115**, 1880–1885.
- Schmid, H., J ager, B., Lohse, J. & Suttrop, M. (2009) Longitudinal growth retardation in a prepubertal girl with chronic myeloid leukemia on long-term imatinib treatment. *Haematologica*, **94**, 1177–1179.
- Schultheis, B., Nijmeijer, B.A., Yin, H., Gosden, R.G. & Melo, J.V. (2012) Imatinib mesylate at therapeutic doses has no impact on folliculogenesis or spermatogenesis in a leukaemic mouse model. *Leukemia Research*, **36**, 271–274.
- Setty, B.A., Hayani, K.C., Sharon, B.I. & Schmidt, M.L. (2009) Prolonged chronic phase of greater than 10 years of chronic myelogenous leukemia in a patient with congenital human immunodeficiency virus infection. *Pediatric Blood & Cancer*, **53**, 658–660.
- Shah, N.P., Kim, D.W., Kantarjian, H., Rousselot, P., Llacer, P.E., Enrico, A., Vela-Ojeda, J., Silver, R.T., Khoury, H.J., Muller, M.C., Lambert, A., Matloub, Y. & Hochhaus, A. (2010) Potent, transient inhibition of BCR-ABL with dasatinib 100 mg daily achieves rapid and durable cytogenetic responses and high transformation-free survival rates in chronic phase chronic myeloid leukemia patients with resistance, suboptimal response or intolerance to imatinib. *Haematologica*, **95**, 232–240.

## Guideline

- Sherbenou, D.W., Wong, M.J., Humayun, A., McGreevey, L.S., Harrell, P., Yang, R., Mauro, M., Heinrich, M.C., Press, R.D., Druker, B.J. & Deininger, M.W. (2007) Mutations of the BCR-ABL-kinase domain occur in a minority of patients with stable complete cytogenetic response to imatinib. *Leukemia*, **21**, 489–493.
- Shima, H., Tokuyama, M., Tanizawa, A., Tono, C., Hamamoto, K., Muramatsu, H., Watanabe, A., Hotta, N., Ito, M., Kurosawa, H., Kato, K., Tsurusawa, M., Horibe, K. & Shimada, H. (2011) Distinct impact of imatinib on growth at prepubertal and pubertal ages of children with chronic myeloid leukemia. *Journal of Pediatrics*, **159**, 676–681.
- Silver, R.T., Woolf, S.H., Hehlmann, R., Appelbaum, F.R., Anderson, J., Bennett, C., Goldman, J.M., Guilhot, F., Kantarjian, H.M., Lichtin, A.E., Talpaz, M. & Tura, S. (1999) An evidence-based analysis of the effect of busulfan, hydroxyurea, interferon, and allogeneic bone marrow transplantation in treating the chronic phase of chronic myeloid leukemia: developed for the American Society of Hematology. *Blood*, **94**, 1517–1536.
- Sokal, J.E., Baccarani, M., Tura, S., Fiacchini, M., Cervantes, F., Rozman, C., Gomez, G.A., Galton, D.A., Canellos, G.P., Braun, T.J., Clarkson, B.D., Carbonell, F., Heimpel, H., Extra, J.M., Fiere, D., Nissen, N.I., Robertson, J.E. & Cox, E.B. (1985) Prognostic discrimination among younger patients with chronic granulocytic leukemia: relevance to bone marrow transplantation. *Blood*, **66**, 1352–1357.
- Soverini, S., Martinelli, G., Amabile, M., Poerio, A., Bianchini, M., Rosti, G., Pane, F., Saglio, G. & Baccarani, M. (2004) Denaturing-HPLC-based assay for detection of ABL mutations in chronic myeloid leukemia patients resistant to imatinib. *Clinical Chemistry*, **50**, 1203–1213.
- Soverini, S., Martinelli, G., Rosti, G., Bassi, S., Amabile, M., Poerio, A., Giannini, B., Trabacchi, E., Castagnetti, F., Testoni, N., Luatti, S., de Lavallade, A., Cilloni, D., Izzo, B., Fava, M., Abruzzese, E., Alberti, D., Pane, F., Saglio, G. & Baccarani, M. (2005) ABL mutations in late chronic phase chronic myeloid leukemia patients with up-front cytogenetic resistance to imatinib are associated with a greater likelihood of progression to blast crisis and shorter survival: a study by the GIMEMA Working Party on Chronic Myeloid Leukemia. *Journal of Clinical Oncology*, **23**, 4100–4109.
- Soverini, S., Gnani, A., Colarossi, S., Castagnetti, F., Abruzzese, E., Paolini, S., Merante, S., Orlandi, E., de Matteis, S., Gozzini, A., Iacobucci, I., Palandri, F., Gugliotta, G., Papayannidis, C., Poerio, A., Amabile, M., Cilloni, D., Rosti, G., Baccarani, M. & Martinelli, G. (2009) Philadelphia-positive patients who already harbor imatinib-resistant Bcr-Abl kinase domain mutations have a higher likelihood of developing additional mutations associated with resistance to second- or third-line tyrosine kinase inhibitors. *Blood*, **114**, 2168–2171.
- Soverini, S., Hochhaus, A., Nicolini, F.E., Gruber, F., Lange, T., Saglio, G., Pane, F., Muller, M.C., Ernst, T., Rosti, G., Porkka, K., Baccarani, M., Cross, N.C. & Martinelli, G. (2011) BCR-ABL kinase domain mutation analysis in chronic myeloid leukemia patients treated with tyrosine kinase inhibitors: recommendations from an expert panel on behalf of European Leukemia-Net. *Blood*, **118**, 1208–1215.
- Suttorp, M. & Millot, F. (2010) Treatment of pediatric chronic myeloid leukemia in the year 2010: use of tyrosine kinase inhibitors and stem-cell transplantation. *Hematology – American Society of Hematology Educational Program*, **2010**, 368–376.
- Suttorp, M., Thiede, C., Tauer, J.T., Roettgers, S., Sedlacek, P. & Harbott, J. (2009a) Chronic myeloid leukemia in pediatrics – first results from study CML-PAED II. (Abstract). *Blood*, **114**, 145.
- Suttorp, M., Claviez, A., Bader, P., Peters, C., Gadner, H., Ebell, W., Dilloo, D., Kremens, B., Kabisch, H., Fuhrer, M., Zintl, F., Gobel, U. & Klingebiel, T. (2009b) Allogeneic stem cell transplantation for pediatric and adolescent patients with CML: results from the prospective trial CML-paed I. *Klinische Padiatrie*, **221**, 351–357.
- Vandyke, K., Dewar, A.L., Fitter, S., Meticanin, D., To, L.B., Hughes, T.P. & Zannettino, A.C. (2009) Imatinib mesylate causes growth plate closure in vivo. *Leukemia*, **23**, 2155–2159.
- Wadhwa, J., Szydlo, R.M., Apperley, J.F., Chase, A., Bua, M., Marin, D., Olavarria, E., Kanfer, E. & Goldman, J.M. (2002) Factors affecting duration of survival after onset of blastic transformation of chronic myeloid leukemia. *Blood*, **99**, 2304–2309.
- Willis, S.G., Lange, T., Demehri, S., Otto, S., Crossman, L., Niederwieser, D., Stoffregen, E.P., McWeeney, S., Kovacs, I., Park, B., Druker, B.J. & Deininger, M.W. (2005) High-sensitivity detection of BCR-ABL kinase domain mutations in imatinib-naïve patients: correlation with clonal cytogenetic evolution but not response to therapy. *Blood*, **106**, 2128–2137.

## Appendix I

### Scoring systems applied for CML chronic phase at diagnosis in adult patients

Scoring systems established in adult medicine to estimate the risk of progression in CML CP during subsequent treatment. This can be applied at diagnosis only and scoring must be performed before any treatment is commenced [Sokal: treatment with hydroxycarbamide; Hasford: treatment with interferon-alpha; EUROpean Treatment Outcome Study (EUTOS): treatment with imatinib].

	Sokal score*†	Sokal score young adults*‡	Hasford/EURO score†§	EUTOS score†
Variables, unit				
Age, years	0.0116 × (age – 43.4)		0.6666 [if age >50 years]	
Spleen, cm below costal margin	+0.0345 × (spleen size – 7.51)	+0.0255 (spleen size – 8–14)	+0.042 × spleen size	(4 × spleen size)
Platelet count, ×10 <sup>9</sup> /l	+0.188 × ([platelets/700] <sup>2</sup> – 0.563)	+0.1025 × ([platelets/700] <sup>2</sup> – 0.627]	+1.0956 [if platelets >1 500 000]	
Blood blasts, %	+0.0887 × (blasts – 2.1)	+0.0324 × (blasts – 2.22)	+0.0584 × blasts	
Blood basophils, %			+0.2039 [if basophils >3]	+(7 × basophils)
Blood eosinophils, %			+0.0413 × eosinophils	
Haematocrit (Hct)		–0.0173 (Hct – 34.2)		
Sex (male = +1.0; female = +2.0)		–0.2682 (Sex – 1.40)		

## Appendix I . (Continued)

	Sokal score*†	Sokal score young adults*‡	Hasford/EURO score†§	EUTOS score†
Relative risk				
Low risk	<0.8	<0.8	<780	≤87
Intermediate risk	0.8–1.2	0.8–1.2	781–1480	
High risk	>1.2	>1.2	>1480	>87

\*Sokal risk is expressed as exponential of the total.

†Calculator available online at [http://www.leukemia-net.org/content/leukemias/cml/cml\\_score/](http://www.leukemia-net.org/content/leukemias/cml/cml_score/). The main differences between the EURO and Sokal scores concern age (it is more important in the Hasford/EURO than in Sokal), spleen size, and the percentage of blasts in peripheral blood (more important in Sokal than in Hasford/EURO).

‡Calculated from a cohort of 625 patients (25 patients <16 years; 249 patients aged 16–30 years and 351 patients aged 31–45 years): survival was 6.0 years for the low risk group, 4.8 years for the intermediate risk group and 3.0 years for the high risk group (Sokal *et al*, 1985).

§Hasford risk is expressed as the total × 1000.

## Appendix II Imatinib drug interactions

Drugs known to interact with the same CYP450 isoenzymes (2D6 and 3A4) as imatinib should be used with caution. Special care has to be given to the concomitant use of paracetamol. Prophylactic anti-emetics should be withheld until the patient has experienced grade 1 nausea or vomiting.

CYP450 isoenzyme	Substrates	Inhibitors	Inducers	Markers
CYP2D6	Antidepressants	Ajmaline	None known	Debrisoquine
	Neuroleptics	Chinoidine		
	Beta-blockers	Fluoxetine		
	Antiarrhythmics	Paroxetine		
	Codeine	Quinidine		
	Dextromethorphan	Ritonavir		
	Ethylmorphine			
	Nicotine			
CYP3A4	Paracetamol	Clotrimazole	Dexamethasone	Dapsone
	Carbamazepine	Ketoconazole	Phenytoin	Erythromycin
	Ciclosporin	Ritonavir	Rifampin	Ketoconazole
	Digitoxin	Troleandomycin	Troleandomycin	Lidocaine
	Diazepam			
	Erythromycin			
	Felodipine			
	Fluoxetine			
	Nifedipine			
	Quinidine			
	Saquinavir			
	Steroids			
	Terfenadine			
	Triazolam			
	Verapamil			
	Warfarin			