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22 (known as a Philadelphia (Ph) chromosome), which leads to the creation of a fusion protein expressed from the fusion gene formed by juxtaposition of parts of the BCR (breakpoint cluster region) and ABL1 (Abelson 1) genes. The resulting oncoprotein is a constitutively active tyrosine kinase and appears to operate as an initiator for the development of the leukaemia. It is not known why this precise translocation occurs recurrently. Clinical features, diagnosis, and (historical) prognosis Clinical features—many patients are asymptomatic at diagnosis, which is made following a routine blood test. Others present with signs and symptoms including fatigue, sweats, fever, weight loss, haemorrhagic manifestations, and abdominal discomfort (due to splenomegaly). Diagnosis—this is typically made by the examination of a periph- eral blood film (revealing features including increased numbers of neutrophils, eosinophils, basophils, immature myeloid cells, and, in some cases, platelets) and the demonstration of the Ph chromosome by conventional cytogenetics in a bone marrow aspirate or periph- eral blood sample. Polymerase chain reaction analysis of peripheral blood confirms the presence of a BCR-ABL1 transcript and charac- terizes the BCR-ABL1 junction. Prognosis—before the introduction of tyrosine kinase inhibitors (TKIs) the condition, having usually been diagnosed in the chronic phase, then spontaneously progressed after (typically) 3 to 6 years to myeloid (or less commonly lymphoid) blast transformation, which had a very poor prognosis. This has changed significantly since the introduction of TKIs. Treatment The

original TKI, imatinib, has had a very significant impact on
the first-line management of patients with CML. It induces durable complete cytogenetic responses in the majority of patients and prolongs overall survival substantially. Although the incidence is - unchanged, the improvement in survival resulting from TKI treatment has led to an ever increasing prevalence of this form of leukaemia. Imatinib, however, does not totally eradicate the leukaemia in most cases and therapy is usually lifelong. Second- and third-generation TKIs, including dasatinib, nilotinib, bosutinib, and ponatinib,
show enhanced potency against BCR-ABL1 activity and are licensed within Europe for first-line (dasatinib, nilotinib, bosutinib) or second-line or subsequent (dasatinib, nilotinib, bosutinib, ponatinib) use in CML. Patients with suboptimal responses to first- line treatment can be offered (1) a different second-line TKI; or (2) a third-line TKI, such as ponatinib; or (3) allogeneic stem cell transplantation—for patients less than 65 years of age and with a suitable donor. A second indication to switch TKI is drug intoler- ance and each agent is associated with a range of similar and nonoverlapping toxicities, although cardiovascular toxicity appears to be a particular concern for nilotinib and ponatinib, pleural effu- sion and pulmonary arterial hypertension for dasatinib, and diar- rhoea for bosutinib. Introduction Patients with chronic myeloid leukaemia (CML) have been well served by translational research over the past half century. Though the disease was first described in 1845 and characterized by the 1920s, it was a further 60 years before the unravelling of initiating molecular events paved the way to define specific targets for treat- ment. CML is a clonal disease that results from an acquired mo- lecular change in a pluripotent haematopoietic stem cell. The leukaemia cells have a consistent cytogenetic abnormality, the Philadelphia (Ph) chromosome, which carries a BCR-ABL1 fusion gene (Fig. 22.3.4.1). This gene encodes a BCR-ABL1 oncoprotein with enhanced tyrosine kinase activity, which is generally con- sidered to be the ‘initiating event’ in the chronic phase of CML, though there remains some debate as to whether this is indeed the first molecular event in all cases. TKIs can inhibit the enzymatic activity of the dysregulated BCR-ABL1 tyrosine kinase and have now become the preferred treatment for all newly diagnosed patients with CML, including children. TKIs substantially reduce the number of leukaemia cells in a patient’s body, and comparison with historical data confirms the notion that they prolong overall survival very substantially, leading to an increased prevalence of the disease. However, very deep molecular responses (MR4.5, 4.5-log reduction in BCR-ABL1 transcripts from baseline) occur in only a minority of patients, and allogeneic stem cell transplantation (alloSCT) remains the only treatment that can reliably produce complete and durable MR4.5 due presumably to eradication of all residual leukaemia stem cells. The authors and editors gratefully acknowledge the inclusion in this chapter of material contributed to previous editions of the Oxford Textbook of Medicine by Tariq I. Mughal and John M. Goldman (who died on 24 December 2013). † It is with great regret that we report that Tessa L. Holyoake died on 30 August, 2017. 22q-(Ph) bcr-abl1 abl 22 bcr 9 9q+ Expresses a fusion protein with tyrosine kinase activity abl-bcr Fig. 22.3.4.1
A schematic representation of how the t(9;22) translocation produces the Philadelphia (Ph) chromosome.

 More recently, TKI discontinuation trials have been conducted for patients achieving MR4.5 (and in some cases less deep molecular response) and consistently demonstrate that around 40% of pa- tients in deep molecular remission (at least MR4) can safely stop a TKI without suffering an inevitable relapse. These studies are cur- rently being extended worldwide with results eagerly awaited. The second-generation TKIs, notably dasatinib, nilotinib and bosutinib, have become firmly established in clinical use for the treatment of imatinib-

resistant/refractory CML and Ph-positive acute lympho- blastic leukaemia (ALL) and are now used by many specialists for first-line treatment also. Epidemiology The annual incidence of CML is constant worldwide at about 1 to 2 per 100 000 of the population per annum. In the Western world, it represents approximately 15% of all adult leukaemias and less than 5% of all childhood leukaemias, although these figures are changing because of the increasing prevalence of CML resulting from suc- cessful therapy. In the Western world, the median age of onset is 50 to 60 years, and there is a slight male excess. In contrast, the median age of onset may be considerably younger in some other countries, such as India. Importantly, as we become more successful in treating this rare malignancy, the annual CML-related death rates are declining fur- ther: the current estimate is around 2% and this predicts that the prevalence will plateau at around 35 times the incidence by 2050 (Fig. 22.3.4.2). Aetiology For most patients with CML, possibly for all, there appear to be no obvious predisposing factors, and the disease arises sporadically. Epidemiology studies have suggested a marginal increment in the number of cases of CML following exposure to high doses of irradi- ation as occurred in survivors of the Hiroshima and Nagasaki atomic bombs in 1945. A small number of families with a high incidence of the disease have also been reported, though no specific HLA geno- types have been identified. One convincing case has been reported of CML recurring in cells of donor origin following related alloSCT. Natural history CML is a remarkably heterogeneous disease. Before the introduc- tion of TKIs, it typically ran a biphasic or triphasic course. It was usually diagnosed in the chronic phase, which typically lasted 3 to 6 years; the leukaemia then spontaneously progressed to blast trans- formation. About 70 to 80% of patients had a myeloid blast trans- formation, and they usually survived 2 to 6 months; the 20 to 30% of patients with a lymphoid blast transformation had a slightly better survival. About half the patients in the chronic phase transformed directly into blast transformation, and the remainder did so fol- lowing a period of accelerated phase. Soon after the introduction of imatinib, it was observed that the natural history for most patients with CML who received this drug as initial therapy, particularly for patients who remain in complete cytogenetic response (CCyR) beyond the fourth year of therapy, 200000 180000 160000 140000 120000 100000 Number of cases 80000 60000 40000 20000 2000 2005 2010 2015 2020 2025 Year 2030 2035 2040 2045 2050 Prevalence Fig. 22.3.4.2 Estimated prevalence of CML in the United States of America. Reproduced with permission from Huang X, Cortes J, Kantarjian H (2012). Estimations of the increasing prevalence and plateau prevalence of chronic myeloid leukemia in the era of tyrosine kinase inhibitor therapy. Cancer, 118, 3123–7. Copyright © 2012, John Wiley and Sons.

 was very greatly improved. The 8-year follow-up of a phase III pro- spective trial, the International Randomized Study of Interferon plus Cytarabine vs STI571 (IRIS), which compared imatinib to the previous best nontransplant therapy, interferon-α (IFN-α) and cytarabine, showed that 55% of the original cohort randomized to receive the imatinib were still taking the drug and the majority was still in CCyR 8 years after starting treatment (Fig. 22.3.4.3 and Table 22.3.4.1). Patients presenting in the late chronic phase appear to fare less well, and those in the advanced phases, particularly the blast phase, generally do poorly, including those who did initially respond to imatinib. In patients with lymphoid blast phase CML, there appear to be no durable responses beyond 6 months. Clinical features and diagnosis Current estimates suggest that one-third to one-half of patients with CML are totally asymptomatic at diagnosis, which is made following a routine blood test. The remainder present with signs and symptoms often of about 3 months’ duration and related to altered haemopoiesis, particularly anaemia and platelet dysfunction and increasing disease burden, resulting in splenomegaly. Most patients will have

leucocytosis due to increased numbers of myeloid cells at all stages of maturation; basophilia is almost universal, and some pa- tients have an eosinophilia (Box 22.3.4.1). The anaemia tends to be mild and normochromic normocytic in nature; some patients have 3.3 7.5 4.8 1.7 0.8 0.3 1.5 2.8 1.8 0.9 0.5 0 0 1 2 3 4 5 6 7 8 With Event % Event: Loss of CHR Loss of MCyR, AP/BC Death during treatment AP/BC Year 6 7 8 5 4 3 2 1 1.4 0 1.3 0.4 Fig. 22.3.4.3 IRIS 8-year follow-up. Loss of response or progression events are early (years 1–4) and decline thereafter. CHR, complete haematological response; MCyR, major cytogenetic response; AP/BC, accelerated phase/blast crisis. Source data from Deininger, M, et al. (2009). International Randomized Study of Interferon Vs STI571 (IRIS) 8-Year Follow up: Sustained Survival and Low Risk for Progression or Events in Patients with Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP) Treated with Imatinib, Blood, 114, 1126. Table 22.3.4.1 The 8-year follow-up results of the IRIS trial Still on first-line imatinib 304 (55%) Discontinued imatinib 249 (45%) Adverse events/abnormal labs 30 (5.4%) Suboptimal response 77 (13.9%) Death 16 (2.9%) SCT 16 (2.9%) Withdrawal consent 44 (8.0%) No reconsent to amendment 19 (3.4%) Crossed over to IFN + Ara-Ca 14 (2.5%) Other reasonsb 3 (6.0%) Ara-C, cytosine arabinoside; IFN, interferon; SCT, stem cell transplantation. a Due to intolerance (0.7%), lack of minor cytogenetic response at 12 months or progression (1.8%). b Includes administrative problems, protocol violation, lost to follow-up. Box 22.3.4.1 WHO criteria for accelerated and blast phases of CML CML, accelerated phase (AP) Diagnose if one or more of the following is present: • Blasts 10 to 19% of peripheral blood white cells or bone marrow cells. • Peripheral blood basophils at least 20%. • Persistent thrombocytopenia (<100 × 109/litre) unrelated to therapy, or persistent thrombocytosis (>1000 × 109/litre) unresponsive to therapy. • Increasing spleen size and increasing white blood cell count unre- sponsive to therapy. • Cytogenetic evidence of clonal evolution (i.e. the appearance of an additional genetic abnormality that was not present in the initial spe- cimen at the time of diagnosis of chronic phase CML). • Megakaryocytic proliferation in sizable sheets and clusters, associated with marked reticulin or collagen fibrosis, and/or severe granulocytic dysplasia, should be considered as suggestive of CML-AP. These findings have not yet been analysed in large clinical studies, however, so it is not clear if they are independent criteria for accelerated phase. They often occur simultaneously with one or more of the other features listed. CML, blast phase (BP) Diagnose if one or more of the following is present: • Blasts 20% or more of peripheral blood white cells or bone marrow cells. • Extramedullary blast proliferation. • Large foci or clusters of blasts in bone marrow biopsy. Source data from Vardiman, JW (2008). Chronic myelogenous leukaemia, BCR-ABL1 positive. WHO classification of tumours of haematopoietic and lymphoid tissues, 32–37.

 a degree of thrombocytosis. Nearly all patients diagnosed in the ad- vanced phases of CML are symptomatic. Occasionally patients may present with extramedullary disease, such as a chloroma. Classical clinical features include sweats, weight loss, haemor- rhagic manifestations, such as spontaneous bruising and retinal haemorrhages, abdominal discomfort due to splenomegaly, fatigue (often but not always related to anaemia), and fever (Box 22.3.4.2). The diagnosis is typically made by the examination of a peripheral blood film and the demonstration of the Ph chromosome by conven- tional cytogenetics on a bone marrow aspirate sample. Most haema- tologists also carry out a bone marrow trephine examination; this is often hypercellular with complete or near complete loss of fat spaces and a high myeloid to erythroid ratio. The presence of less than 10% of blast cells is compatible with chronic disease, but a higher per- centage suggests that the patient may be in accelerated or blast phase (Fig. 22.3.4.4). Sometimes the diagnosis is made by demonstrating the presence of a BCR-ABL1 gene by

fluorescence in situ hybridization on a per- ipheral blood sample. Modern practice dictates the use of a baseline real-time quantitative polymerase chain reaction analysis of periph- eral blood to confirm the presence of a BCR-ABL1 gene and charac- terize the BCR-ABL1 junction. Such an analysis is particularly useful in the subsequent monitoring of patients. Molecular biology The Ph chromosome is an acquired cytogenetic abnormality pre- sent in all leukaemic cells of the myeloid lineage and in some B- cells. It is formed as a result of a reciprocal translocation of DNA from chromosomes 9 and 22, t(9; 22)(q34;q11) (Fig. 22.3.4.1). The classical Ph chromosome is easily identified in about 90% of CML patients. A further 5% of patients have variant translocations in which chromosomes 9, 22, and other additional chromosomes are involved. About 5% of patients with clinical and haematological fea- tures typical of CML lack the Ph chromosome and are referred to as having ‘Ph-negative’ CML. These patients have a BCR-ABL1 chi- meric gene and are referred to as Ph-negative, BCR-ABL1-positive cases. Patients who are BCR-ABL1 negative are not considered to have CML but an unclassified form of myeloproliferative disorder. Some patients acquire additional clonal cytogenetic abnormal- ities, in particular +8, +Ph, iso17q–, and +19, as their disease pro- gresses. The emergence of such clones may herald the onset of blast transformation. The various genetic events have now been elucidated, and the chimeric BCR-ABL1 gene is believed to play a central role in the pathogenesis of CML, though the precise mechanism(s) are still not fully understood. Three distinct breakpoint locations in the BCR gene in chromosome 22 have been identified (Fig. 22.3.4.5). The break in the major breakpoint cluster region (M-bcr) occurs in the intron between exon e13 and e14 or in the intron between exon e14 and e15 (toward the telomere). By contrast, the position of the breakpoint in the ABL1 gene on chromosome 9 is highly vari- able and may occur at almost any position upstream of exon a2. The Ph translocation results in the juxtaposition of 5′ sequences from the BCR gene with 3′ sequences from the ABL1 gene. This event results in the generation of the chimeric BCR-ABL1 fusion gene transcribed as an 8.5-kbp mRNA. This mRNA encodes a pro- tein of 210 kDa (p210BCR-ABL1) that has a greater tyrosine kinase activity compared with the normal ABL protein. The different breakpoints in the M-bcr result in two slightly different chimeric BCR-ABL1 genes, resulting in either an e13a2 or an e14a2 tran- script. The type of BCR-ABL1 transcript has no important prog- nostic significance. Box 22.3.4.2 Clinical features of patients with chronic phase CML seen at the Hammersmith Hospital, London • Fatigue: 33.5% • Bleeding: 21.3% • Weight loss: 20.0% • Abdominal discomfort (left upper quadrant): 18.6% • Sweats: 14.6% • Bone pain: 7.4% • Splenomegaly: 75.8% • Hepatomegaly: 2.2% Adapted with permission from Savage D, et al. (1997). Clinical features at diagnosis in 430 patients with chronic myeloid leukaemia seen at a referral centre over a 16-year period. Br J Haematol, 96, 111–16. Fig. 22.3.4.4 A peripheral blood film from a patient with CML in chronic phase. Alternative fusion genes in CML BCR-ABL1 mRNAs e14a2 e13a2 11 a2 e14 e13 e12 1 1 e12 e13 a2 e1 e1 ABL1 BCR kinase domain Oncoproteins p210BCR-ABL1 Fig. 22.3.4.5 The various breakpoints identified in the CML.

 The second breakpoint location in the BCR gene occurs be- tween exons e1 and e2 in an area designated the minor breakpoint cluster region (m-bcr) and forms a smaller BCR-ABL1 fusion gene. This is transcribed as an e1a2 mRNA which encodes a p190BCR-ABL1 oncoprotein. This protein characterizes about two-thirds of patients with Ph-positive ALL. A third breakpoint location is found in pa- tients with the very rare Ph-positive chronic neutrophilic leukaemia. This has been designated as a micro breakpoint cluster region (μ-bcr) and results in e19a2 mRNA, which encodes a larger protein of 230 kDa (p230BCR-ABL1). The recognition of several features in the BCR-ABL1 oncoprotein that are essential for cellular

transformation led to the identifi- cation of signal transduction pathways activated in BCR-ABL1-positive cells (Fig. 22.3.4.6). Much attention has since focused on determining the precise role played by the various BCR-ABL1 downstream proteins in the pathogenesis of CML. A number of possible mechanisms of BCR-ABL1-mediated malignant transform- ation have been implicated, which are not necessarily mutually ex- clusive. These include constitutive activation of mitogenic signalling, reduced apoptosis, impaired adhesion of cells to the stroma and extracellular matrix, and proteasome-mediated degradation of ABL inhibitory proteins. The deregulation of the ABL tyrosine kinase facilitates autophosphorylation, resulting in a marked increase of phosphotyrosine on BCR-ABL1 itself, which creates binding sites for the SH2 domains of other proteins. A variety of such substrates, which can be tyrosine phosphorylated, have now been identified. Although much is known of the abnormal interactions between the BCR-ABL1 oncoprotein and other cytoplasmic molecules, the finer details of the pathways through which the 'rogue' proliferative signal is mediated, such as the RAS-MAP kinase, JAK-STAT, and the PI3 kinase pathways, are incomplete, and the relative contributions to the leukaemic 'phenotype' are still unknown. Moreover, the multiple signals initiated by the BCR-ABL1 oncoprotein have both prolif- erative and antiapoptotic qualities, which are often difficult to sep- arate. Much remains to be learned about the significance of tyrosine phosphatases in the transformation process. It is generally believed that some CML stem cells, at a cytokinetic level, transit through a 'quiescent' or 'dormant' (G0) phase. These quiescent CML cells appear to be able to shift between quiescence and active cycling, allowing them to proliferate under certain cir- cumstances. There is also evidence that some Ph-positive cells are quiescent and less likely to be eradicated by cycle-dependent cyto- toxic drugs, even at high doses, or indeed by any of the currently available TKIs. It is likely that the acquisition of a BCR-ABL1 fusion gene by a haemopoietic stem cell and the ensuing expansion of the Ph-positive clone sets the scene for acquisition and expansion of one or more Ph-positive subclones that are genetically more aggressive than the original Ph-positive population. The propensity of the Ph-positive clone to acquire such additional genetic changes is an example of 'genomic instability', but the molecular mechanisms underlying this instability are poorly defined. Such new events may occur in the BCR-ABL1 fusion gene or indeed in other genes in the Ph-positive population of cells and presumably underlie the progression to ad- vanced phases of the disease. The average length of chromosomal telomeres in the Ph-positive cells is generally less than that in cor- responding normal cells, and the enzyme telomerase, which is re- quired to maintain the length of telomere, is up-regulated as the patient's disease enters the advanced phases. About 25% of patients with CML in myeloid blast transformation have point mutations or Haematopoietic stem cell (a) (b) JAK2 JAK2 BCR-ABL GRB2-SOS Ras-GTP Raf-MEK-ERK GRB2-SOS Ras-GTP Raf-MEK-ERK mTOR PI3K mTOR PI3K STAT5 STAT5 Transcription of target genes for differentiation or proliferation Transcription of target genes for inhibition of apoptosis or drug resistance CML cell Fig. 22.3.4.6 Signal transduction pathways which are potentially important in CML in chronic phase. BCR-ABL1 enables JAK2-independent phosphorylation of downstream pathways. Reprinted by permission from Springer Nature: Fabbro D (2012). BCR-ABL signaling: A new STATus in CML. Nat Chem Biol, 8, 228–9.

 deletions in the p53 gene, and about half of all patients in lymphoid blast transformation show homozygous deletion in the p16 gene. There is also evidence supporting the role of the RB (retinoblastoma) and the MYC genes in disease progression. In the future, whole- genome and targeted exome sequencing should largely clarify the mutational landscape of CML, whether it differs between patients, and how that then modifies the response

to TKIs. Prognostic factors Various efforts have been made to establish criteria definable at diagnosis, both prognostic (disease related) and predictive (treatment related), that may help to predict survival for individual patients. Historically, the most frequently used method was that proposed by Sokal in 1984, whereby patients can be divided into various risk categories based on a mathematical formula that takes into account the patient's age, blast cell percentage, spleen size, and platelet count at diagnosis. The Euro or Hasford system is an updated Sokal index, which includes consideration of basophil and eosinophil num- bers. Stratifying patients into good-, intermediate-, and poor-risk categories may assist in the decision-making process regarding appropriate treatment options. Recent observations, however, suggest that age per se might not influence the biology of the disease, but ra- ther increases the probability of treatment-related adverse effects by virtue of potential comorbid conditions. In 2011, Hasford and col- leagues proposed a new prognostic score, European Treatment and Outcome Study (EUTOS), which requires only an assessment of the spleen size and percent basophils in blood. This method has since been validated and found to be predictive for CCyR, progression- free survival, and overall survival in an independent large series of patients treated with first-line imatinib outside of prospective studies (Table 22.3.4.2). More recently, the response to TKIs at a given time point is being increasingly used to assess prognosis (and response). Several inves- tigators have identified BCR-ABL1 transcript numbers at 3 months following the initiation of treatment as the single most important prognostic factor (Table 22.3.4.3). This has been included in the National Comprehensive Cancer Network (NCCN) 2019 treatment guidelines in the United States of America and the updated 2013 European LeukemiaNet recommendations. More recently, rather than use an individual time point, the rate of decline or halving time in the early period after start of TKI has been assessed and may prove even more useful. Management First-line therapy Clearly TKIs have had a significant impact on the worldwide standard practice to treat patients with CML. Until 2000, it was con- ventional to recommend an alloSCT to all patients younger than 50 years of age with newly diagnosed CML in the chronic phase, pro- vided they had suitable HLA-identical sibling or 'matched' unrelated donors. Patients presenting in the advanced phases of CML usually received combination chemotherapy, often followed by an alloSCT if a 'second' chronic phase could be achieved. The treatment algorithm for newly diagnosed patients changed dramatically once the impres- sive success of imatinib in inducing durable CCyR in the majority of newly diagnosed patients with CML in the chronic phase was recognized. Worldwide, imatinib, or one of the second-generation TKIs (nilotinib, bosutinib or dasatinib), are now the preferred treat- ment for most, if not all, newly diagnosed patients with CML in the chronic phase, and are also useful in the management of patients presenting in the advanced phase Fig. 22.3.4.7. Importantly, the question whether an adult patient should start with imatinib (at the 'standard' dose), or dasatinib, bosutinib or nilotinib cannot be resolved at present. We have approaching 20 years of experience with imatinib and the drug's unprecedented clinical success is notable; however, despite approaching 15 years of experience with dasatinib and nilotinib, although we see convincing evidence of more rapid and deeper molecular responses, this has not translated into a convincing improvement in overall survival. Even longer-term follow-up with assessment of side effects is needed to address the issue of preferred first-line therapy. The current indica- tions for alloSCT are summarized in Table 22.3.4.4. Imatinib, a 2-phenylaminopyrimidine, inhibits the enzymatic ac- tion of the activated BCR-ABL1 tyrosine kinase by occupying the ATP-binding pocket of the kinase component of the BCR-ABL1 oncoprotein, thereby blocking the capacity of the enzyme to phos- phorylate and activate downstream effector molecules that cause the leukaemic phenotype. It also binds to an adjacent part of the kinase domain in a manner that holds the ABL activation loop of the

oncoprotein in an inactive configuration. Imatinib induces ‘cumulative best’ CCyR in 82% of all previously untreated patients with CML in the chronic phase. About 2% of all patients in the chronic phase progress to advanced phase disease each year, which contrasts with estimated annual progression rates for historical therapies of more than 15% for patients treated with hydroxycarbamide and about 10% for patients receiving IFN-α, either with or without cytarabine. The event-free survival was 83% and the estimated overall survival was 93% (corrected for CML-related deaths only; Fig. 22.3.4.8), confirming that imatinib prolongs overall survival very substantially compared with historical patients who received IFN-α or hydroxycarbamide.
A substantial proportion of the patients in CCyR also achieve at least a 3-log reduction in BCR-AB1 transcripts (major molecular response (MMR)), and this proportion seems to have continued to increase steadily with time on imatinib; a small minority of patients achieve MR4.5. The standard starting dose of imatinib is 400 mg/day, although several single-arm studies suggest that higher doses, up to 800 mg/ day, might give better results with a greater proportion of pa- tients achieving CCyR and MMR. Such studies also suggest better Table 22.3.4.2 Prediction of prognosis Sokal 1984 EURO 1998 EUTOS 2011 Parameters Age Age Spleen Spleen Spleen Blasts Blasts Platelets Platelets Eosinophils Basophils Basophils Treatment Chemotherapy IFN Imatinib Endpoint Survival Survival CCyR, survival

 progression-free survival and transformation-free survival but with potentially more side effects, particularly myelosuppression. The safety analysis of imatinib is also quite impressive, with very few potentially serious long-term side effects. When imatinib is used at the standard starting dose of 400 mg/day, side effects in- clude nausea, headache, various skin reactions, infraorbital oe- dema, bone pains, and sometimes, generalized fluid retention. Significant cytopenias and hepatotoxicity occur less commonly and usually in the first 6 to 12 months of therapy. Very rare cases of severe or fatal cerebral oedema have been reported, and there have been some concerns about potential cardiomyopathy, although the longer-term (8 years) IRIS study analysis reassures us that this is not a major problem, except for older patients, who might have other predisposing cardiac risks and have anaemia. Another con- cern is the potential teratogenicity of imatinib. One study assessing outcomes in 125 of 180 study patients exposed to the agent during pregnancy concluded that about half of the offspring born were normal; 28% of the study cohort elected to undergo termination of pregnancy, including three after identification of fetal abnor- malities. In total, there were 12 infants in whom abnormalities were identified, including three who had strikingly similar com- plex malformations. It would therefore appear sensible to avoid imatinib exposure during pregnancy. However, there appear to be no risks of fetal malformations of children from men taking imatinib at the time of conception.
Second-generation TKIs as potential first-line therapy Following the successful treatment of patients with CML in chronic phase resistant/refractory or intolerant to imatinib, dasatinib, nilotinib, and bosutinib entered clinical trials for first-line therapy of the newly diagnosed patient. Dasatinib at a dose of 100 mg once daily was tested in a trial known as Dasatinib versus Imatinib Study in Treatment-Naïve CML Patients (DASISION), nilotinib at two dosages, either 300 or 400 mg twice daily in the Evaluating Nilotinib Efficacy and Safety in Newly Diagnosed Patients (ENESTnd), and bosutinib at a dose of 500 mg once daily in the Bosutinib Safety and Efficacy in Newly Diagnosed CML (BELA) trial. Dasatinib and nilotinib received regulatory approval for first-line therapy following the initial results in 2010. Table 22.3.4.5 depicts the current results of IRIS, DASISION, ENESTnd, and BELA at 12, 24, and 60 months (where available). Currently dasatinib is recommended at a dose of 100 mg once daily, nilotinib at 300 mg twice daily and bosutinib 400 mg once daily

(following a second trial called BFORE) in the first-line setting. Overall, the results reported suggest that frontline therapy with dasatinib, nilotinib (at either dose) or bosutinib, renders higher response rates with a comparable toxicity profile compared to imatinib with up to 60 months of follow-up. It remains unknown whether these higher rates of early response will translate into improved event-free and/or overall survival. Thus far, no statistically signifi- cant differences in survival have been observed. It is of course of Table 22.3.4.3 Early (3-month) response, rate of decline and outcome in chronic phase CML Drug Response at 3 months Level Outcomes Reference IM MR 10% IS OS, PFS, CCyR, MR4.5 Marin et al. J Clin Oncol, 2012, 30, 232–6 IM MR 10% IS OS Hanfstein et al. Leukemia, 2012, 9, 2096–102 NIL second line MR 10% IS CCyR, MMR, EFS Branford et al. J Clin Oncol, 2012, 30, 4323–9 IM MR 0.35-fold of baseline by 3 months OS Hanfstein et al. Leukemia, 2014, 10, 1988–92 EFS, event-free survival; IM, imatinib; IS, International scale; MR, molecular response; NIL, nilotinib; MMR, major molecular response; MR4.5, undetectable disease in cDNA with

> 32 000 ABL control transcripts; OS, overall survival; PFS, progression-free survival. 1.0 0.9 0.8 0.7 0.6 0.5 0.4 0.3 0.2 0.1 0.0 0 2 4 6 8 10 12 14 Year after diagnosis n = 3615 (CMLI, II) Imatinib, 2002–2011 (CML IV) 5–year survival 90% 8–year survival 88% IFN or SCT, 1997–2003 (CML IIIA) 5–year survival 71% IFN or SCT, 1995–2001 (CML III) 5–year survival 63% IFN ,1986–1994 5–year survival 53% Busulfan, 1983–1994 5-year survival 38% Hydroxyurea, 1983–1994 5-yr surv. 44% Survival probability 16 18 20 22 24 26 Fig. 22.3.4.7 Improvement of survival of CML by therapy 1983–2011. Courtesy of Professor Rudiger Hehlmann and German CML Study Group.

SECTION 22 Haematological disorders 5220 Estimated overall survival at 8 years was 93%, considering only CML-related deaths, and 85% for all deaths 100 90 80 70 60 50 40 30 20 10 0 0 12 24 36 Months since randomization 48 60 72 84 96 108 Survival: deaths associated with CML Overall survival Fig. 22.3.4.8 Leukaemia-free survival in patients with CML based on the IRIS trial (an intention to treat analysis). Courtesy of Professor Michael Deininger, presented at ASH 2009. Table 22.3.4.5 Results of clinical trials of imatinib, dasatinib, nilotinib, and bosutinib as initial therapy in CML in chronic phase Trial N Response rates (intention to treat) 12 months 24 months 60 months CCyR MMR MR4.5 CCyR MMR MR4.5 CCyR MMR MR4.5 IRISa Imatinib 400 mg od 553 69% NA NA 73% NA NA 87% NA NA DASISIONb Dasatinib 100 mg od 259 85% 46% NA 85% 64% 17% 83% 76% 42% Imatinib 400 mg od 260 73% 28% NA 82% 46% 8% 78% 64% 33% ENESTndc Nilotinib 300 mg bd 282 65% 55% 11% 87% 71% 26% NA 77% 54% Nilotinib 400 mg bd 281 55% 51% 7% 85% 67% 21% NA 77% 52% Imatinib 400 mg od 283 22% 27% 1% 77% 44% 10% NA 60% 31% BELAd Bosutinib 500 mg od 250 70% 41% NA 79% 59% NA NA NA NA Imatinib 400 mg od 252 68% 27% NA 80% 49% NA NA NA NA bd, twice daily; CCyR, complete cytogenetic remission; MMR, major molecular response; MR4.5, undetectable disease in cDNA with >32 000 ABL control transcripts; N, number of patients; NA, not applicable; od, once daily. a IRIS Trial: Druker BJ, et al. N Engl J Med, 2006, 355, 2408–17. b DASISION Trial: Kantarjian HM, et al. Blood, 2012, 119, 1123–9. c ENESTnd Trial: Larson RA, et al. Leukemia, 2012, 26, 2197–203. d BELA Trail: Brummendorf TH, et al. Br J Haematology, 2015, 168, 69–81. Table 22.3.4.4 Potential indications for an alloSCT in CML in 2019 First chronic phase Third line after failure of and/or intolerance to two TKIs T315I mutation

and not optimally responding to ponatinib Accelerated phase De novo accelerated phase at diagnosis: alloSCT recommended for all patients that do not achieve an optimal response to TKIs Progression to accelerated phase from chronic phase on TKI: alloSCT recommended once disease control re-established Blast crisis Urgently in all eligible patients once chronic phase is re-established with TKI or chemotherapy; consider second- or third-generation TKI post allograft (maintenance) AlloSCT is not recommended in uncontrolled resistant blast phase CML

22.3.4 Chronic myeloid leukaemia 5221 considerable interest that almost twice the number of patients treated with dasatinib or nilotinib achieved an MR4.5 compared to imatinib and therefore might be candidates for treatment discontinuation in the future. Despite showing superior molecular responses compared to imatinib in the first line, bosutinib 500 mg daily failed to achieve its primary endpoint of superior CCyR in the BELA study. However, a second study comparing imatinib with bosutinib 400 mg daily (BFORE) has shown superior cytogenetic and molecular responses compared to imatinib. The European LeukemiaNet has published recommendations for optimal response, warning features and treatment failure for chronic phase CML patients treated with TKIs. These guidelines were last updated in 2013 (Table 22.3.4.6). The challenge of how long to continue imatinib in optimally re- sponding patients remains unresolved at present. For patients who achieve a durable MR4.5, stopping the drug in the context of a clinical trial is reasonable. Several clinical trials (STIM, TWISTER, STOP 2G TKI, and EUROSKI) have all reported successful discontinu- ation of therapy in a subgroup of patients who have responded op- timally to their TKI and have been in a stable MR4.5 for a prolonged period. In the French STIM study, in which imatinib was discon- tinued in CML patients who had undetectable BCR-ABL transcripts for at least 2 years, 39% of patients did not develop molecular relapse and remained with undetectable transcripts (Fig. 22.3.4.9). Similar results were obtained in the Australian TWISTER study with 47.1% of patients who had sustained undetectable transcripts obtaining a stable treatment-free remission. Interestingly, the majority of re- lapses in both studies occurred within the first 6 months of stopping imatinib. These important results raise the possibility that imatinib is able to eradicate CML in some cases, but not in others. More recent studies (STOP 2G TKI and EUROSKI) have used loss of MMR as the trigger for restarting therapy. With this approach, treatment-free Table 22.3.4.6 Revised European LeukemiaNet (ELN 2013) criteria for responses in patients with chronic myeloid leukaemia in chronic phase initially treated with TKIs Milestone Response definition and criteria Optimal Warning Failure Baseline NA High risk or ACA/Ph+, major route NA 3 months BCR-ABL1 ≤10% and/or Ph+ ≤35% BCR-ABL1 >10% and/or Ph+ 36–95% No CHR and/or Ph+ >95% 6 months BCR-ABL1 ≤1% and/or Ph+ 0 (CCyR) BCR-ABL1 1-10% and/or Ph+ 1–35% BCR-ABL1 >10% and/or Ph+ >35% 12 months BCR-ABL1 ≤0.1% (MMR) BCR-ABL1 >0.1–1% BCR-ABL1 >1% and/or Ph+ >0 Any time Stable or improving MMR ACA/Ph− (−7 or 7q−) Loss of CHR, loss of CCyR, confirmed loss of MMR, mutations, ACA in Ph+ cells ACA, additional cytogenetic abnormalities; CHR, complete haematological response; NA, not applicable; Ph+, Philadelphia chromosome positive. Baccarani M, et al. (2013). Blood, 122, 872–84. 0 0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0 3 6 9 12 15 18 21 Months (m) since discontinuation of imatinib 56 had a recurrence (loss of CMR) within the first 6 months and one at M7 one at M19 and at M24 At 18 months 43% (95% confidence interval [CI]: 33–52) Survival without molecular relapse 24 27 30 33 36 Fig. 22.3.4.9 Preliminary Kaplan–Meier estimates of sustained complete molecular response (CMR) after discontinuation of imatinib from the French STIM (Stop Imatinib) study. For 100 patients, the estimated molecular relapse-free survival is 45% (95% CI 34–55%) at 6 months, 43% (33–53%) at 12 months, 41% (34–55%) at 24 months, and 35% (22–46%) at 30 months. Adapted from Lancet Oncology, Vol. 11, Mahon FX,

et al., 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, Pages 1029–35, Copyright © 2010, with permission from Elsevier.

SECTION 22 Haematological disorders 5222 remission rates are higher, 61% at 12 months and 57% at 24 months in the STOP 2G TKI study and similar results at 12 months in the EUROSKI trial. The STIM study identified patients with a low Sokal risk score, male sex, and longer duration of imatinib treatment as potential prognostic factors for the maintenance of treatment-free remission after discontinuing imatinib, and current research is fo- cusing on identifying factors which will predict maintenance of treatment-free remission. However, unless a TKI cessation clinical trial is available, at present, the best advice for the responding patient is to continue the drug indefinitely. The best initial treatment for children is still uncertain, though most paediatric haematologists would now advocate the use of imatinib in the first instance. For those children failing imatinib, a second-generation TKI (dasatinib or nilotinib) would usually be considered for second-line therapy. AlloSCT would only be con- sidered for treatment failure/multiple intolerances and if the child has a suitable HLA donor available. In addition to the expected side effects also encountered in adults, imatinib can cause significant growth retardation in children. Second-line therapy Definitions of treatment ‘failure’ and ‘warning’ to TKIs are shown in Table 22.3.4.6. Primary resistance or refractoriness to the drug appears to be very rare and when seen may be related to poor drug compliance, poor gastrointestinal absorption, cytochrome P450 polymorphisms, interactions with other medications, and abnormal drug efflux and influx at the cellular level. In a small cohort of patients, a correlation between the expression of human organic cation trans- porter type 1 (hOCT-1) and response has been observed: the higher the levels of OCT-1, the better the molecular responses. Clearly, it is prudent to confirm compliance in all patients in whom resistance is suspected since clinical outcome is known to be adversely affected when adherence is less than 90% (Fig. 22.3.4.10). A somewhat larger proportion of patients, about 20% in the chronic phase, respond initially to imatinib and then lose their response. This acquired or ‘secondary’ resistance results from a variety of mechanisms, including amplification of the BCR-ABL1 fusion gene, relative overexpression of the BCR-ABL1 protein, and expansion of subclones with point mutations in the BCR-ABL1 kinase domain. Such point mutations code for amino acid substitu- tions that may impede binding of imatinib but do not impair phos- phorylation of downstream substrates that mediate the leukaemia signal. The precise position of the mutation appears to dictate the degree of resistance to imatinib; some mutations are associated with minor degrees of drug resistance, whereas one notorious mu-tation, the replacement of threonine by isoleucine at position 315 (T315I), is associated with near-total unresponsiveness to imatinib, dasatinib, nilotinib, and bosutinib. The precise clinical significance and indeed the kinetics of the over 100 currently well-characterized mutations remain largely unknown (Fig. 22.3.4.11). The majority of patients who are resistant/intolerant to imatinib should receive dasatinib, nilotinib or bosutinib (Fig. 22.3.4.12). For those patients demonstrating resistance to first-line therapy with nilotinib, dasatinib or bosutinib, an alternative second-generation TKI (nilotinib, dasatinib, or bosutinib) should be considered. Currently, ponatinib should be reserved for third-line therapy or those with a demonstrable T315I mutation in which case it should be considered for any line of therapy. Dasatinib is a thiazole-carboxamide structurally unrelated to imatinib. Furthermore, it binds to the ABL kinase domain regard- less of the conformation of the activation loop—whether open or closed. It also inhibits some of the Src family kinases. Preclinical studies showed that dasatinib is 300-fold more potent than imatinib and is active against 18 of 19 tested imatinib-resistant kinase do- main mutant subclones, with the

notable exception of the T315I 1.0 (a) (b) (c) P < .001 0.9 0.8 Time Since Start of Imatinib Therapy (months) Probability of MMR 0.7 0.6 0.5 0.4 0.3 0.2 0.1 0 6 12 18 24 30 36 42 48 54 60 66 72 1.0 P < .001 0.9 0.8 Time Since Start of Imatinib Therapy (months) Probability of 4-Log Reduction 0.7 0.6 0.5 0.4 0.3 0.2 0.1 0 6 12 18 24 30 36 42 48 54 60 66 72 1.0 P < .002 0.9 0.8 Time Since Start of Imatinib Therapy (months) Probability of CMR 0.7 0.6 0.5 0.4 0.3 0.2 0.1 0 6 12 18 24 30 36 42 48 54 60 66 72 Adherence > 90% (n = 64) Adherence ≤ 90% (n = 23) Adherence > 90% (n = 64) Adherence ≤ 90% (n = 23) Adherence > 90% (n = 64) Adherence ≤ 90% (n = 23) Fig. 22.3.4.10 Six-year probability of major molecular response (MMR) according to measured adherence to treatment. From Marin D, et al. (2010). Adherence is the critical factor for achieving molecular responses in patients with chronic myeloid leukemia who achieve complete cytogenetic responses on imatinib. J Clin Oncol, 28, 2381–8.

22.3.4 Chronic myeloid leukaemia 5223 1242T M244V K247R L248V G250E/R Q252R/H Y253F/H E255K/V M237V P-loop SH3 contact SH2 contact A-loop E258D W261L L273M E275K/Q V299L The 10 most frequent mutations, accounting for ~70% of resistance cases, are highlighted in red L298V I293V E292V/Q Y342H M343T A344V A350V M351T E355D/G/A V379I A380T F382L L384M L387M/F/V M388L Y393C H396P/R/A A397P M472I P480L F486S E507G D276G T277A E279K V280A V289A/I F311L/I T315I F317L/V/1/C Y320C L324Q F359V/1/C/L D363Y L3641 A365V A366G L370P V371A E373K S417F/Y I418S/V A433T S438C E450K/G/A/V E453G/K/V/Q E459K/V/G/Q Fig. 22.3.4.11 A schematic depiction of some of the currently established ABL1 kinase domain mutations. Courtesy of Dr Simona Soverini. N N N Imatinib (Gleevec, STI-571) Nilotinib (Tasigna, AMN107) Bosutinib (SKI-606) Dasatinib (Sprycel, BMS-354825) Ponatinib H N H N H N H N H N H N N N N N N OH N O O Cl Cl O CN HN N N S O Cl O N N N N N O F N N F F N H N O CF3 N N N N Fig. 22.3.4.12 BCR-ABL1 inhibitors: imatinib, nilotinib, dasatinib, bosutinib, and ponatinib.

SECTION 22 Haematological disorders 5224 mutant. Current experience with dasatinib in patients with chronic phase CML resistant/refractory to imatinib suggests that about 90% of the patients have a complete haematological response and 52% have a CCyR. About 25% of patients with the more advanced phases of CML and Ph-positive ALL also achieve reasonable responses. Haematological toxicities are common, particularly in those with advanced phases of CML and Ph-positive ALL. These include neutropenia (49%), thrombocytopenia (48%), and anaemia (20%). Nonhaematological toxicities include diarrhoea, headaches, superfi- cial oedema, pleural effusions, occasional pericardial effusions, and pulmonary arterial hypertension (rare, c.1%). Grade 3/4 side effects are rare, and grade 3/4 pleural effusions occur in less than 10% of patients. Dasatinib has also been tested in patients with CML in advanced phases whose disease was resistant to both imatinib and nilotinib; remarkably, 57% of patients achieved haematological responses. Among those patients who had a haematological response, 32% had a cytogenetic response, including two patients who achieved CCyR. However, these responses are seldom durable in blast phase or in Ph-positive ALL, with the majority of patients developing resistance within 6 months. In advanced phase CML, the dasatinib dose is ei- ther 140 mg once daily or 70 mg twice daily. Nilotinib, like imatinib, acts by binding to the closed (inactive) conformation of the ABL kinase domain, but with a much higher affinity. Like imatinib, it inhibits the deregulated tyrosine kinase activity of ABL by occupying the ATP-binding pocket of the oncoprotein and blocking the capacity of the enzyme to phos- phorylate downstream effector molecules. In vitro studies suggest that nilotinib is about 30- to 50-fold more potent than imatinib. Nilotinib is also active in 32 of 33 imatinib-resistant cell lines with mutant ABL kinases, but like imatinib and dasatinib has no ac- tivity against the Bcr-Abl1T315I

mutation. Phase II studies in pa- tients who are resistant or intolerant to imatinib show a CCyR rate of 45% at 4 years and progression-free survival of 57%. Nilotinib is recommended at a dose of 400 mg twice daily second line. Patients in the advanced phases of CML also respond, but to a lesser degree. The most common treatment-related toxicity is myelosuppression, followed by headaches, pruritus, and rashes. Overall, 22% of the patients in the chronic phase experienced thrombocytopenia, with 19% having either grade 3 or 4 severity; 16% had neutropenia and a further 16% had anaemia. Most of the nonhaematological adverse effects were of a grade 1/2 severity. More recently, arterial thrombotic events and onset of diabetes/ metabolic syndrome have been described with nilotinib therapy and caution should be taken when commencing nilotinib in pa- tients with cardiovascular risk factors or pre-existing diabetes. It is recommended that all patients should have a cardiovascular risk assessment, including blood pressure measurement, lipids, glucose, and HbA1c prior to commencing nilotinib and at least annually thereafter. Third-line therapy Bosutinib (formerly SKI-606), an oral dual ABL and SRC inhibitor, is chemically different from both dasatinib and nilotinib. Following single-arm studies in patients with CML in all phases intolerant or resistant to one or more TKI, it was noted that 53.4% of the study co- hort achieved a durable major cytogenetic response. Grade 3 to 4 side effects included diarrhoea, anaphylactic shock, myelosuppression, fluid retention, hepatotoxicity, and rash. Based on these results, the drug was approved for the treatment of adult CML patients with chronic phase or advanced phase disease who were resistant to prior therapy. Ponatinib (formerly AP24534) is a third-generation TKI which has an interesting chemical structure based on a purine scaffold and a central triple carbon–carbon bond with a substructure that is similar to imatinib. The drug inhibits ABL, SRC, FLT3, and a var- iety of other kinases. It was developed initially for patients who were considered to have become resistant to TKIs as a result of a T315I subclone and subsequently, in a phase II trial, found to have consid- erable activity in all patients with CML who were resistant/refractory or indeed intolerant to prior TKIs, including imatinib, dasatinib, and/or nilotinib. Like nilotinib, ponatinib has been associated with a significant number of arterial thrombotic events, which led to it being temporarily withdrawn by the Food and Drug Administration in 2013. In addition, a phase III trial assessing its candidacy as first- line therapy, compared to imatinib was abandoned due to concerns about cardiovascular toxicity. The indications for alloSCT are shown in Table 22.3.4.4. For pa- tients who are resistant/refractory to two or more TKIs, and are under the age of 65 years, it is probably best to consider an alloSCT, provided a suitable donor is identified and the patient remains in the chronic phase of the disease. A risk score has been developed by the European Society for Blood and Marrow Transplantation (EBMT) which is helpful in determining those patients that may benefit from an alloSCT (Fig. 22.3.4.13). It is also timely to note that as our nontransplant efforts to improve CML patients' outcomes have im- proved, there have been some improvements in transplant outcomes also (Figs. 22.3.4.14 and 22.3.4.15). Patients who proceed to a transplant should stop the TKI at least 2 weeks prior to the transplant. Current data also suggest that prior treatment with any TKI does not increase the probability of transplant-related mortality, but clearly our experience with alloSCT following any TKI is still limited and we should continue to be vigi- lant. Moreover, patients with kinase domain mutations appear to fare as well post-transplant as those lacking such mutations. Advanced phase CML For those with advanced phase disease, the choice of treatment is de- pendent on whether this arises de novo or as a result of progression from chronic phase CML while on TKI therapy. Current European LeukemiaNet guidelines recommend either imatinib 400 mg twice daily or dasatinib 70 mg twice daily or 140 mg once daily for treat- ment of de novo advanced phase CML. AlloSCT is recommended for all blast phase patients and accelerated phase patients without an optimal response who have a suitable donor. Additional conven- tional

chemotherapy may be required for disease control prior to alloSCT. For patients progressing to accelerated or blast phase CML while on TKI therapy, further therapy should be with any TKI not previously used and ponatinib for cases with the T315I mutation. All eligible patients should then proceed to alloSCT; and conventional chemotherapy is frequently required for disease control in this poor risk group of patients. None of the currently available agents has made a major impact in this area, in particular for patients who are in lymphoid blast crisis.

22.3.4 Chronic myeloid leukaemia 5225 Investigational approaches Immunotherapy Following the realization that a molecular remission and ‘cure’ might not be possible with imatinib alone in the majority of patients, many efforts were directed to exploring the potential of developing an active specific immunotherapy strategy for patients with CML by inducing an immune response to a tumour-specific or tumour- associated antigen. The principle involves generating an immune re- sponse to the unique amino acid sequence of p210 at the fusion point. Clinical responses to the BCR-ABL1 peptide vaccination, including CCyR, have been reported in a small series. In contrast to previous earlier unsuccessful attempts, administration of granulocyte– macrophage colony-stimulating factor was included as an immune adjuvant, and patients were only enrolled if they had measurable residual disease and human leucocyte antigen known to which the selected fusion peptides were predicted to bind avidly. However, these results have not been confirmed in other studies, and the con- tinuing success of TKIs has resulted in limited development of other approaches. Nonetheless, vaccine development against BCR-ABL1 and other CML-specific antigens could become an attractive treat- ment for patients who have a minimal residual disease status with TKIs as a potential additional strategy to enable treatment-free re- mission. Other targets for vaccine therapy studied include peptides derived from the Wilms tumour 1 protein, proteinase 3, and elastase, all of which are overexpressed in CML cells. Furthermore, interferon is also considered to have an immunological mode of action and superior responses to the combination of imatinib and pegylated interferon compared to imatinib alone were demonstrated in the 100 Donor HLA identical sibling Unrelated donor First chronic phase Accelerated phase Blast crisis <20 years 20–40 years

> 40 Years All, except: Male recipient/female donor <12 months 12 months 1 0 1 0 2 1 0 2 1 0 1 0 Stage Age Score 0 or 1 (n = 634) Score 2 (n = 881) Score 5–7 (n = 275) Score 4 (n = 485) Score 3 (n = 867) Sex match Time to transplantation Survival Variable Categories Score 75 50 25 0 0 12 Survival probability (%) 24 36 48 60 72 84 Fig. 22.3.4.13 Transplantation risk: EBMT score. Adapted from The Lancet, Vol. 352, Gratwohl A, et al., Risk assessment for patients with chronic myeloid leukaemia before allogeneic blood or marrow transplantation, Pages 1087–92, Copyright © 1988, with permission from Elsevier. Overall survival among good risk patients (score = 0, 1) N = 645 2000–2003 1991–1999 1980–1990 1.0 0.9 0.8 0.7 0.6 0.5 0.4 0.3 0.2 0.1 0.0 0 24 48 72 96 120 144 168 192 216 240 months N = 1466 N = 594 Fig. 22.3.4.14 Improvements in survival rates by decades of transplantation for patients with CML in chronic phase. The EBMT registry data; courtesy of the EBMT Group. 100 80 60 40 20 0 0 1 2 P<.001 Score = >4 (N = 34) Score = 2 (N = 35) Score = 0.1 (N = 18) Score = 3 (N = 41) Score = 4 (N = 45) 3 4 5 6 Years post SCT Probability of survival % 7 8

9 10 Fig. 22.3.4.15 Survival of patients allografted for CML at the Hammersmith Hospital, London, from January 2000 to December 2010 stratified by EBMT risk score. Reproduced, with permission, from Pavlu J, et al. (2011). Blood 117(3), 755–63.

SECTION 22 Haematological disorders 5226 French SPIRIT trial. Unfortunately, many patients find interferon difficult to tolerate, limiting its utility in this setting. Investigational drugs Other specific inhibitors of signal transduction pathways downstream of BCR-ABL1 have been tested alone and in combination with TKIs in vitro. However, in chronic phase in particular, translation of these effective combinations into successful clinical trials has been dif- ficult due to concerns about side effects. Recently, early-phase clin- ical trials of SMO inhibitors (inhibiting the developmental hedgehog pathway which is upregulated in many cancers) in combination with various TKIs in resistant CML closed early due to poor recruitment, lack of efficacy and an unacceptable side effect profile. The phase II CHOICES clinical trial which evaluated the autophagy inhibitor hydroxychloroquine in combination with imatinib in patients with detectable transcripts has recently closed to recruitment. Asciminib, (ABL001), an allosteric inhibitor of BCR-ABL, is currently in a phase II clinical trials alone or in combination with other TKIs. Omacetaxine mepesuccinate (formerly homoharringtonine) is a semisynthetic plant alkaloid (cetaxine) that enhances apoptosis of CML cells, and is active in combination with imatinib in drug-resistant/refractory pa- tients, including those who harbour the T315I mutation. Other po- tential agents include rapamycin, an mTOR inhibitor, venetoclax, a BCL-2 inhibitor, idasanutlin, an MDM2 inhibitor, tazemetostat, an EZH2 inhibitor, and ruxolitinib, a Janus kinase inhibitor. Conclusion The substantial understanding of the molecular features and patho- genesis of CML has provided important insights into targeting treat- ment to specific molecular defects. The successful introduction of TKIs, commencing with imatinib and now with the addition of dasatinib and nilotinib, as targeted therapy for CML has made the approach to management of the newly diagnosed patient fairly com- plex. Furthermore, a third second-generation TKI, bosutinib, and a third-generation TKI, ponatinib, have significant activity in selected patients in both chronic and the more advanced phases of the dis- ease, who are resistant to imatinib, dasatinib, and/or nilotinib. For the moment, the various treatment options should be assessed carefully in terms of the relative risk:benefit ratios, and a manage- ment strategy should be developed accordingly. Consideration of long-term side effects, particularly cardiovascular events is developing increasing prominence with nilotinib and ponatinib in particular. With increasing data demonstrating the safety and efficacy of imatinib in particular, early alloSCT should no longer be considered in any patient cohort, other than in exceptional cir- cumstances. Newly diagnosed chronic phase patients should com- mence either imatinib 400 mg once daily, nilotinib 300 mg twice daily, dasatinib 100 mg once daily, or bosutinib 400 mg once daily, with regular review and cytogenetic/molecular testing to ensure they are achieving treatment milestones. It is important to consider that although nilotinib, dasatinib and bosutinib result in superior cytogenetic and molecular responses, compared to imatinib, there is no current evidence that they prolong life any more than imatinib. Patients who are resistant/refractory to imatinib, dasatinib, or nilotinib should probably receive bosutinib or ponatinib (including those with the T315I mutation in particular), and/or be considered for an alloSCT provided that a suitable donor is identified. As we see more patients obtaining more rapid and deeper molecular re- sponses, it is likely that the criteria for an optimal response and treat- ment failure will become more stringent with a view to obtaining a future treatment-free remission for as many patients as possible. FURTHER READING

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