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Review

Chronic myeloid leukaemia: STI 571 magnifies the therapeutic dilemma

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1. Introduction

Chronic myeloid leukaemia (CML) is a clonal multilineage myeloproliferative disorder, which originates in a single abnormal haemopoietic stem cell. It involves myeloid, monocytic, erythyroid, megakaryocytic and B-lymphoid lineages and to some extent the T-lymphoid lineage [1]. Although the disease was first described in the English literature in 1845, the first important landmark in its study did not occur until 1960 when Nowell and Hungerford discovered in leukaemia cells a consistent cytogenetic abnormality, later designated the Philadelphia (Ph) chromosome [2]. It was subsequently established that the Ph chromosome was associated with genetic events that cause CML and thus CML became the first human cancer in which a specific cytogenetic abnormality could be linked to its pathogenesis. Thereafter, there was rapid progress in the understanding of the molecular biology of CML and some of the changes underlying the chronic phase of CML that occur at the DNA level have now been fully elucidated.

Until the 1980s, CML had been regarded as inexorably fatal. Thereafter it gradually became clear that allogeneic haemopoietic stem cell transplantation (SCT) could cure some (but not all) of the patients submitted to this treatment. About the same time, it was shown that interferon-alpha (IFNα) could suppress the proliferation of CML cells and prolong survival. In the late 1980s, adoptive immunotherapy with alloreactive lymphocytes was introduced as treatment for patients who relapsed following an allogeneic SCT [3]. Most recently the tyrosine kinase inhibitor, STI 571, has shown great promise in early studies, but its role in treating newly diagnosed patient is not yet defined. The decision as how best to treat the newly diagnosed patient with CML has therefore become exceedingly complex and is discussed in this review.

2. Natural history

Characteristically, CML is a biphasic or triphasic disease with most patients presenting in the initial stable 'chronic' phase (CP), which lasts typically 3–6 years. The natural history of CML involves spontaneous progression to a more 'advanced' phase, a term that includes the 'accelerated' phase and 'blast crisis'. Approximately half of all patients in chronic phase 'transform' directly into blast crisis and the remainder do so following an intervening period of accelerated phase of variable duration. In the advanced disease, the CML cells fail to mature and when blast crisis occurs the predominating cells in the blood and marrow resemble either the myeloblasts (myeloid blast transformation) or the lymphoblasts (lymphoid blast transformation) found in patients with acute leukaemias.

3. Molecular biology

The Ph chromosome is an acquired cytogenetic abnormality present in all CML cells (Fig. 1). It is formed as a result of a reciprocal translocation of genetic material from the long arm of one chromosome 9 and the long arm of one chromosome 22, referred to as t(9;22)(q34;q11). This translocation results in the juxtaposition of 3′ sequences from the *ABL* (Abelson) protooncogene gene normally present on chromosome 9 with the 5′ sequences of the truncated *BCR* (breakpoint cluster region) gene that remain on chromosome 22. This event generates the chimeric *BCR-ABL* fusion gene [4].

The classical Ph chromosome can be identified in around 85% of patients who satisfy haematological

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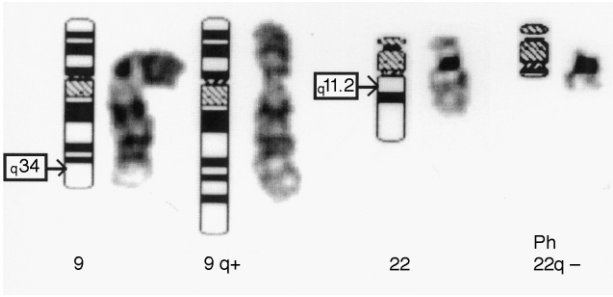

Fig. 1. Partial karyotype of the Philadelphia chromosome translocation t(9;22)(q34;q11) showing the breakpoints on chromosomes 9 and 22.

criteria for CML. In a further 5% of the patients, the translocation is complex, usually involving three or more chromosomes, including the 9 and 22. In about 10% of patients, no Ph chromosome can be identified by conventional cytogenetics; within this cohort, about 40% have an occult *BCR-ABL* chimeric gene, usually located on a normal appearing chromosome 22, but very occasionally located on chromosome 9. The remaining 6% of patients are Ph-negative, *BCR-ABL*-negative and in some of these mutations have been identified in other genes [5]. It is probable that these last patients have a more aggressive clinical course than those with Ph-negative, *BCR-ABL*-positive disease. As the disease progresses Ph-positive patients may acquire additional cytogenetic abnormalities, including duplication of the Ph chromosome, trisomy 8 and iso-chromosome 17q. Mutations or deletions of tumour suppressor genes such as *p16* and *TP53* may also contribute to the disease progression [6].

The *BCR-ABL* fusion gene transcribes a mRNA which encodes a protein that has a much greater tyrosine kinase activity than the normal ABL protein. Depending on the site of the breakpoint in the *BCR* gene, the fusion protein can vary in size from 190 kD to 230 kD (Fig. 2). Three separate breakpoint locations on the *BCR* gene have been identified and rather confusingly termed M-*BCR*, m-*BCR* and μ-*BCR*, respectively [7]. The break in the major breakpoint cluster region (M-*BCR*) occurs nearly always in the intron between exons e13 and e14 (previously referred to as exons b2 and b3) or in the intron between exons e14 and e15 (previously b3 and b4). By contrast, the position of the breakpoint in the *ABL* gene is highly variable and may occur at almost any position upstream of exon a2. Most CML patients with the classical Ph chromosome express a protein of 210 kD ($p210^{BCR-ABL}$). In contrast, a break in the first intron of the *BCR* gene, in an area designated the minor breakpoint cluster region (m-*BCR*) between exons e1 and e2, results in the transcription of an e1a2 mRNA which encodes a protein of 190 kD ($p190^{BCR-ABL}$). This is found in about two-thirds of patients with Ph-positive acute lymphoblastic leukaemia [8]. The third break in the *BCR* gene occurs between exons e19 and e20, in an area designated the micro breakpoint cluster region (μ-*BCR*). The mRNA product, e19a2, encodes a larger protein of 230kD ($p230^{BCR-ABL}$), which is found in those very rare cases of chronic neutrophilic leukaemia associated with a Ph chromosome [9].

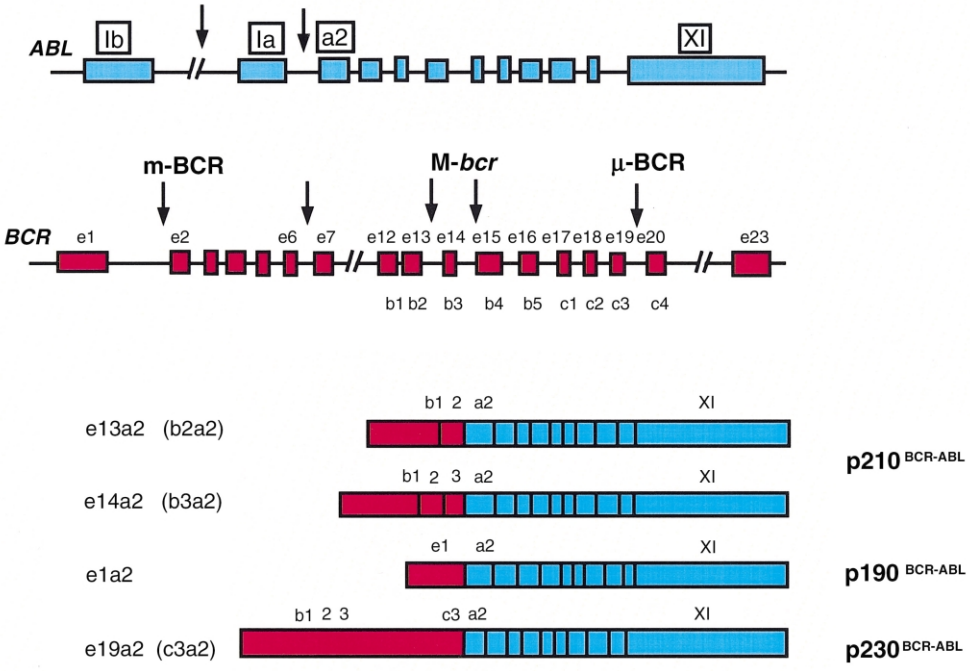

Fig. 2. Schematic representation of the various breakpoints in the *ABL* and *BCR* genes and the encoded proteins in the BCR-ABL positive leukaemias.

The different breakpoints within the M-*BCR* result in two slightly different chimeric *BCR-ABL* transcripts. A break occurring in the intron between exons e13 and e14 yields e13a2 (or b2a2) mRNA, whereas a break occurring in the intron between exons e14 and e15 produces an e14a2 (b3a2) mRNA. Most CML patients have either e13a2 or e14a2 transcripts, but in about 10% of cases both transcripts are present. The type of *BCR-ABL* transcript has no important prognostic significance, except for a higher platelet count in patients with the e14a2 transcripts [10].

Much attention has focused on determining what role the various BCR-ABL proteins play in the pathogenesis of CML. Currently, three possible mechanisms have been implicated, and are not necessarily mutually exclusive [11]. These are constitutive activation of mitogenic signalling, reduced adhesion of cells to the stroma and extracellular matrix, and reduced apoptosis. Although much is known of the abnormal interactions between the BCR-ABL oncoprotein and other cytoplasmic molecules, the precise 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 (Fig. 3).

Normal haemopoietic stem cells survive, but must be maintained in a resting state (or 'deep' G_o phase) as a result of the proliferation of CML cells. Under certain circumstances, however, these normal cells can be induced to proliferate and this provides the rationale for autografting as treatment of CML. There is also evidence for a profoundly quiescent subpopulation of primitive progenitor cells that are Ph-positive [12]. This might be one reason why cycle-active cytotoxic drugs alone, even in high doses, usually fail to eradicate the CML clone.

Progression to advanced phases is often heralded by the Ph-positive cell acquiring additional chromosomal changes, presumably as a result of increasing genetic instability. Recently, it has been demonstrated that the length of the telomere in the Ph-positive cells shortens and the enzyme, telomerase, which is required to maintain the length of telomere is upregulated as the patient's disease enters the advanced phases [13]. Telomere length therefore appears to have some prognostic implications. Patients in chronic phase who have longer telomeres tend to fare better, particularly in regards to response to IFN-α [14].

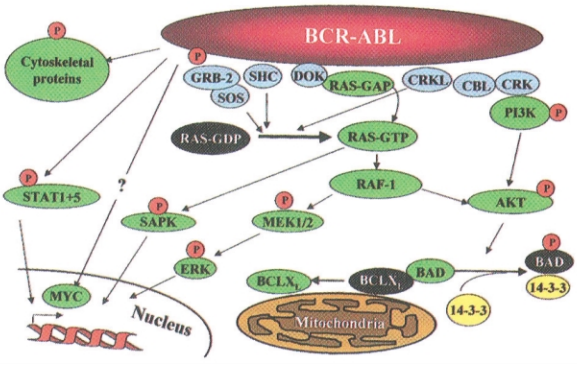

Fig. 3. Signal transduction pathways involved in CML. The diagram shows many, but not all the cytoplasmic molecules known to interact with or to be phosphorylated by the BCR-ABL protein (reproduced from Deininger and colleagues [4] with permission.

4. Clinical features

Most patients typically present with lethargy and anorexia or abdominal discomfort due to splenomegaly, but 30–40% of patients are asymptomatic and the diagnosis is made following a routine blood test. The principal physical finding is a palpable spleen, which is found in up to three-quarters of patients. Hepatomegaly and lymphadenopathy are uncommon. Occasional patients have 'chloromas' or 'granulocytic sarcomas' with subcutaneous deposits of extramedullary leukaemia. In contrast to patients in CP, patients in the advanced phase are often symptomatic with fever, bone pain, bleeding and excessive sweating. Splenic pain due to splenic infarct is not uncommon.

5. Diagnosis

The diagnosis of CML is commonly made by the characteristic appearances of the peripheral blood film and bone marrow trephine biopsy. Cytogenetic analysis for the presence of the Ph chromosome is confirmatory. Molecular studies for the evidence of the BCR-ABL product provide additional confirmation. The peripheral blood usually shows a leucocytosis that involves cells at all stages of differentiation within the myeloid lineage (Fig. 4). Basophilia is an important diagnostic feature as its absence suggests other myeloproliferative disorders, particularly if both the Ph chromosome and *BCR-ABL* gene are absent. Eosinophilia may also be

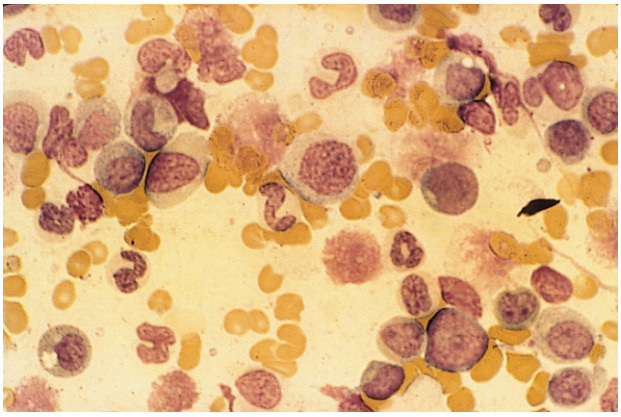

Fig. 4. Peripheral blood film from a patient with CML in chronic phase. CML, chronic myeloid leukaemia.

present but has no diagnostic relevance. There is relative monocytopenia, although absolute numbers may be increased corresponding with the leucocytosis. This differentiates CML from chronic myelomonocytic leukaemia. Thrombocytosis with platelet anisocytosis and nucleated red cells are common.

The bone marrow is markedly hypercellular with loss of normal fat spaces and an increased myeloid to erythroid ratio due to the predominance of myeloid cells, particularly neutrophils and myelocytes. There are no features of abnormal maturation in the precursors. Megakaryocytes are increased and may form clusters, which is less striking than those seen in essential thrombocythaemia. Reticulin fibrosis is usually absent or mildly increased at diagnosis.

6. Prognostic factors

Various efforts have been made to establish criteria definable at diagnosis that may help to predict survival for individual patients. The most frequently used method is that proposed by Sokal and colleagues whereby patients can be divided into various risk categories based on a mathematical formula that takes account of the patient's age, spleen size, percentage of blast cells in the blood and platelet count at diagnosis [15]. Stratifying patients into good, intermediate and poor risk categories may assist in the decision making process regarding appropriate treatment options. Clinically, however, the best prognostic indicator seems to be the response to initial treatment with interferon-alpha (IFN-α); patients who achieve a degree of cytogenetic response have the best survival [16].

7. Management

The recent developments in treatment of patients with CML have made the decisions for individual patients more complicated. Although some patients with CML can be cured by an allogeneic SCT, the risks associated with it need to be carefully assessed. The precise timing of the transplant is still very controversial. The results of allografting have improved in recent years but the non-transplant treatment options have also improved considerably. Thus IFN-α induces haematological control in a significant proportion of patients and confers some improvement in survival, especially for those patients who achieve a degree of cytogenetic response, in comparison with hydroxyurea. It is rare, however, to achieve a molecular remission with IFN-α. The advent of STI 571 offers the prospect of further improvement. It is therefore prudent to discuss the relative merits of the various treatments with the patient at the time of diagnosis and the proposed management strategy.

8. Non-transplant options

8.1. Interferon-alpha

IFN-α, a glycoprotein of biological origin with antiviral and antiproliferative properties, entered clinical trials in the early 1980s and a recent meta-analysis has confirmed the superiority of IFN-α over both busulphan and hydroxyurea [17]. In contrast to busulphan and hydroxyurea, IFN-α treatment resulted in prolongation of survival, in particular for patients achieving major cytogenetic responses [18]. Hochhaus and colleagues assessed the molecular status of patients who achieved complete cytogenetic remissions following IFN-α treatment and found that although the level of residual disease decreased with time, it was rarely completely eliminated [19]. It would therefore be reasonable to continue IFN-α therapy for all patients who achieve a complete cytogenetic response until relatively low levels of residual disease are achieved at a molecular level. Toxicity is common but, in general mild and reversible, with flu-like symptoms being the most common. Less common effects include depression, weight loss, hair loss, various neuropathies and autoimmune-mediated complications, such as thrombocytopenia and hypothyroidism. In an effort to improve the treatment results, current trials are focusing on combining IFN-α with cytotoxic drugs. Data from the French study suggest a higher incidence of cytogenetic response and longer survival using the combination of IFN-α with cytarabine in preference to IFN-α alone [20]. An Italian study showed a similar trend that lacked statistical significance [21]. Finally, the issue of pharmacoeconomic benefit remains unresolved; most published studies suggest only minimal cost-effective benefit [22]. Recently, two types of pegylated IFN-α, one glycosylated and the other not, have entered clinical trials with the primary aim of improving the toxicity profile of 'conventional' IFN-α. An oral preparation of cytarabine (YNK01) is also being investigated in combination with IFN-α.

8.2. Chemotherapy with cytotoxic drugs

Hydroxyurea remains the single most popular cytotoxic drug for the management of CML in CP. Busulphan, much used in the past, is today rarely administered as a single therapy, but may have a role in conjunction with all-*trans* retinoic acid. Homoharringtonine is effective in inducing and maintaining haematological response, but has not been used extensively.

8.3. STI 571

Following the observation that the BCR-ABL protein had a central role in the pathogenesis of CML, efforts

were made to develop molecularly targeted therapies for CML. Since the main transforming property of this protein is thought to reside in its constitutive ABL-associated tyrosine kinase activity, a number of compounds were synthesised to inhibit such action. One such compound is the 2-phenylaminopyrimidine STI 571 (previously known as CGP 57148B). Druker and colleagues showed that STI 571 selectively suppresses the growth of CML cell lines and BCR-ABL positive colony forming units-granulocyte macrophage (CFU-GM) colonies obtained from patients with CML [23].

STI 571 entered clinical trials in 1998 and preliminary results suggest that it is a considerable improvement over IFN-α. More than 90% of patients with CML in chronic phase refractory to IFN-α obtained complete haematological responses during treatment with full doses of STI 571; about 40–45% achieved cytogenetic responses [24]. Patients with CML in myeloid blast crisis also responded, though less durably. STI 571 was administered orally and so far side-effects have been relatively minor. The follow-up is relatively short at present, but if the responses are sustained and confirmed more generally, this novel drug will become the preferred non-transplant treatment option [25]. In conjunction with other methods it will also be useful in the treatment of the more advanced phases of the disease.

Pre-clinical studies have shown that some BCR-ABL positive cells can evade the inhibitory effects of STI 571 by diverse mechanisms. Some of these have now been characterised and include BCR-ABL overexpression as a possible consequence of *BCR-ABL* gene amplification, P-glycoprotein overexpression resulting in the reduction in the uptake of STI 571, or possibly by excessive degradation of the BCR-ABL protein [26]. It is possibly that acquisition of compensatory mutations in genes other than *BCR-ABL* may also be important. Clinically, at present, resistance to STI 571 appears to be rare.

9. Allogeneic stem cell transplantation

9.1. Conventional allografts

Allogeneic SCT using blood- or marrow-derived stem cells from an HLA-identical sibling donor performed in the chronic phase offer a substantial proportion of patients with CML the probability of long-term leukaemia-free survival (LFS) and possibly cure [27,28]. Data collated by the International Bone Marrow Transplant Registry (IBMTR) showed a LFS at 5 years of 55–60% [29]. The probability of relapse at 5 years was 15%. Younger patients fare better than older patients and the results are generally best when the SCT is performed in the early phase of CML. The other major determinants for survival are now reasonably well characterised [30]. These are degree of histo-compatibility between donor and recipient, duration of chronic phase, and gender match of the patient and donor. Gratwohl and colleagues designed a risk assessment model that includes these four major factors that could impact on the probability of survival after transplantation. They ascribed a score for each of these factors and concluded that for patients with all favourable factors, the 5 year LFS is 70–80%, whereas for patients with many poor prognostic factors the LFS was 15–20%.

It is possible that the cytoreductive regimens used prior to the transplant and the preventive measures for graft-versus-host disease (GVHD) also influence the outcome. The cytomegalovirus (CMV) status of the patients is also important; CMV seropositive patients not infrequently reactivate CMV, which may cause clinically significant infection. This may be associated with an increased risk of mortality, especially for the recipients of stem cells from matched unrelated donors [31]. The relative merits of using stem cells derived from bone marrow or peripheral blood are not yet fully established. Blood-derived stem cells result in a faster engraftment and apparently mediate a greater graft-versus leukaemia (GVL) effect compared with the marrow-derived stem cells [32]. However, there appears to be a higher incidence of extensive GVHD after blood stem cell allografts. There has also been some concern that prior treatment with IFN-α might adversely affect the result of a subsequent allograft [33]. Most recently, a German study concluded that if IFN-α was discontinued more than 90 days prior to SCT, no significant adverse effect was noted [34]. It is not known if prior treatment with STI571 might pose similar risks.

In typical family sizes in Europe and North America, only about 30% of patients have one or more genetically HLA-identical siblings and 50% of patients will be too old (> 55 years) for a transplant using conventional age limits. Thus, only 15% of all patients will be eligible for sibling donor transplants. Efforts have therefore focused on the search for suitable volunteer unrelated donors (VUD) and on better conditioning regimens in an attempt to reduce the toxicity. Historically, the results of VUD-SCT have been inferior to those of HLA-matched sibling SCT due to an increased rate of graft failure, GVHD and TRM. Current results of VUD-SCT from the Seattle group for patients with a favourable profile suggest a LFS of 74% at 5 years in patients who are under the age of 50 years and are transplanted within a year of diagnosis [35]. These and other similar results have led to further refinements toward the search for suitable VUDs to make SCT more available [36]. Newer techniques for molecular typing of class I genes should improve the chances of finding phenotypically HLA-matched or acceptably mismatched donors [37].

9.2. Low intensity conditioning (or non-myeloablative) stem cell transplants

The conditioning regimens conventionally used for patients subjected to allogeneic SCT have employed 'myeloablative' doses of chemoradiotherapy designed to eradicate permanently malignant haematopoiesis in the patient and to facilitate the engraftment of donor stem cells. Such regimens are associated with toxicity resulting in significant TRM, particularly in patients older than 50 years of age and in those with co-morbid conditions. Recently, it has been observed that the curative potential of the allograft probably results in large part from an immunologically mediated graft-versus-leukaemia (GVL) effect. This signals an exciting advance in our understanding of how SCT actually works [38]. The most convincing evidence for a GVL effect comes from the observation that donor leucocyte infusions (DLI) can reinduce remissions in patients who have relapsed following allogeneic SCT [39]. This effect has been most notable in patients with CML and multiple myeloma, but is also seen in other haematological malignancies. These observations led to the development of reduced intensity conditioning regimens, which are 'non-myeloablative', but still immunosuppressive [40]. However, although these regimens are well tolerated they are associated with a significant risk for GVHD, which remains a significant cause of mortality and morbidity. Patients who are mixed chimaeras may experience less GVHD compared with full chimaeras, but these patients may also have a diminished potential for the GVL effect, which is necessary for the long-term control of the malignant cells. Mixed chimaeric states can be modified by immune manipulation with DLI or stopping GVHD prophylaxis [41].

Much work still needs to be done to determine the optimal non-myeloablative conditioning regimen for individual patients, in terms of choice of drug, dose given, and drug combinations, all related to the condition under treatment [42]. With a better understanding of the mechanisms of GVHD and the role of T-cell depletion, it will probably be possible to define and expand the T-cell populations that attack tumour tissue, while excluding those T-cell populations that attack normal tissue. At present, there are a number of unresolved issues, some of which are: What should be the upper age limit for non-myeloablative stem cell transplants (NMSCT)? Is radiation therapy essential for the conditioning regimen? Is anti-thymocyte globulin (ATG) necessary? Should T-cell depletion be used and if so, how? How should one monitor chimaerism post NMSCT? How should one monitor minimal residual disease (MRD)? What are the real indications for DLI? Can one use specific cytotoxic T-lymphocytes (CTL)? It will also be important to define the currently used terminologies of 'conventional conditioning', 'reduced conditioning', 'minimal conditioning', 'mini-SCT', 'lite-SCT', 'low intensity conditioning SCT' and 'non-myeloablative SCT' more precisely.

9.3. Treatment of relapse of CML post SCT

Most patients who relapse post allo-SCT do so within the first 3 years. The relapse tends to follow an orderly progression initially with increasing numbers of *BCR-ABL* transcripts by PCR, followed by a cytogenetic relapse and then haematological and clinical relapse [43]. Molecular monitoring of allo-SCT recipients is therefore valuable. For patients with molecular relapse, remission can be induced by withdrawal of immunosuppression or by the transfusion of donor lymphocytes (DLI). DLI can induce remissions in 60–80% of patients with molecular or cytogenetic relapse [39,44]. These important results lend further support to the concept that a GVL effect plays an important role in the cure of CML after allografting. The potential benefit of adding IFN-α to DLI is being assessed at present. Patients who fail to enter remission with DLI may be candidates for a second allo-SCT, but the risk of TRM is relatively high. The 4 year LFS for second allo-SCT is around 30%.

The mechanisms by which T-lymphocytes exert a GVL effect remain speculative. It is possible that they release cytokines, such as interleukin-2, IFN-α or transforming growth factor-α, that selectively suppresses the proliferation of Ph-positive cells. It is possible that T-cells or natural killer cells act directly against leukaemia cells. Perhaps the most attractive possibility is that they recognise tissue-specific alloantigens on host myeloid cells, such as minor histocompatibility antigens or the Wilms tumour 1 antigen [45,46]. Very recently, it was observed that PR1, a proteinase 3-derived peptide, is an important antigen for cytotoxic T lymphocyte immune response against CML [47].

9.4. Autologous stem cell transplantation

Despite the qualified success associated with allo-SCT, the majority of CML patients are not eligible for this therapy. Most patients treated with IFN-α achieve only marginal prolongation in survival compared with hydroxyurea treatment. Autologous SCT following high dose chemotherapy has a relatively TRM and is available to more patients. Retrospective analyses suggest but fall far short of proving that autografting with blood- or marrow-derived stem cells can prolong survival [48,49]. It is recognised that some Ph-negative stem cells survive at the time of diagnosis in most patients lending support to efforts being made to develop techniques that favour reconstitution with Ph-negative haematopoiesis. The Genoa group has pioneered procedures whereby Ph-negative stem cells are har-

vested during the recovery phase after intensive chemotherapy, and demonstrated successful engraftment resulting in Ph-negative haematopoiesis [50].

In most cases, however, the Ph-positive haematopoiesis recurs. This recurrence must be due to residual Ph-positive cells in the patient or in the autografted material and has provided rationale for purging techniques. Various *in vitro* and *in vivo* methods have been developed with variable degree of success. The new generation of *in vitro* purging studies using tyrosine kinase inhibitors targeted against the *BCR-ABL* gene, such as STI 571, may prove more effective.

Although the clinical feasibility and safety of these differing autografting strategies have been demonstrated, the precise therapeutic role of autografting remains unclear. Randomised prospective trials are currently in progress to establish the value of autografting in the treatment of patients with CML.

10. Conclusions and a suggested therapeutic algorithm

The therapeutic advances of the past decade have made the approach to the management of the patients with CML fairly complex. It is wise to discuss the relative merits of various treatment options with the patient at the time of diagnosis and develop a treatment strategy that attempts to balance the patient's likely survival with non-transplant options against the probability of cure after an allogeneic SCT. The encouraging preliminary results obtained with STI 571 and advances in adoptive immunotherapy to activate leukaemia-specific immune response promise to make treatment decisions even more complex in the near future. For the present, for younger patients (e.g. <50 or <55 years) it is reasonable to base a therapeutic strategy on the decision whether to recommend an allogeneic SCT soon after the diagnosis or to offer a trial of IFN-α, or IFN-α plus cytarabine, or possibly STI 571 before allografting. One approach is therefore to define a patient cohort where the risk of TRM is so relatively low that one can reasonably recommend an allogeneic SCT as primary therapy and to define another cohort for which allo-SCT should not be considered in any circumstance. This would leave an intermediate cohort where the advisability of an early transplant is uncertain. Such patients could reasonably receive an initial trial of IFN-α (or in due course of STI 571) and only proceed to allo-SCT if they are deemed to have failed the therapeutic trial. This strategy is illustrated in Fig. 5. Currently patients over the age of 60 years would undoubtedly fall into the 'no allo-SCT' category, but this may change in the near future if further experience confirms the safety and efficacy of low intensity conditioning myeloablative SCT. Finally, one may speculate that conventional allo-SCT could in the future be replaced by a programme of initial treatment with STI 571 in combination with other drugs followed by immunotherapy to eradicate residual disease.

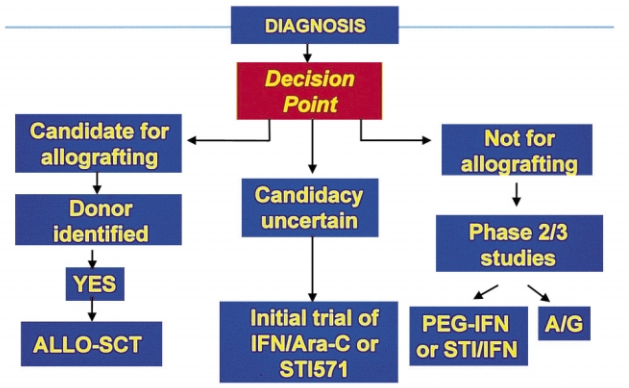

Fig. 5. A suggested algorithm for the management of patients with chronic myeloid leukaemia (CML). PEG-IFN, pegylated interferon alpha; A/G, autograft.

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