PROCEEDINGS ARTICLE

Management of Philadelphia chromosome-positive acute lymphoblastic leukemia

OG Ottmann

Tyrosine kinase inhibitors (TKIs) directed against the ABL kinase are now used routinely during frontline therapy for Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph + ALL) and result in hematologic remission rates exceeding 90%. Minimal residual disease levels are generally lower when TKIs are used in combination with chemotherapy rather than as monotherapy. Although outcome has improved substantially with TKI-based regimens compared with historic controls, allogeneic stem cell transplantation (SCT) in first remission provides the best chance of cure for the majority of patients eligible for SCT. Administration of imatinib after SCT further reduces molecular recurrence and is associated with greatly improved relapse-free and overall survival. The high relapse rate in non-transplanted patients is largely attributable to the emergence of leukemic clones with mutations in the tyrosine kinase domain of BCR-ABL. Ongoing studies with newer TKIs will determine whether these more potent agents are able to sustain remissions without SCT. Assessment of minimal residual disease has become an integral part of the management of Ph + ALL, as it has prognostic importance and is used to guide therapeutic intervention. Novel immunotherapeutic interventions and combinations of TKIs are currently being investigated in clinical trials and may further improve the prognosis of patients with Ph + ALL.

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TYROSINE KINASE INHIBITOR (TKI)-BASED THERAPY FOR NEWLY DIAGNOSED PHILADELPHIA CHROMOSOME-POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA (Ph + ALL)

Administration of the TKI imatinib as frontline treatment of Ph + ALL has increased the rate of complete remissions in newly diagnosed adult patients to approximately 95%. This magnitude of response is achieved irrespective of whether imatinib is given alone or in conjunction with various types of chemotherapy; however, the depth of these responses, as assessed by quantitative determination of Bcr-Abl transcripts, is higher following combined therapy. Although combinations of imatinib with intensive chemotherapy were explored primarily in younger patients and have become the standard approach for patients with *de novo* Ph + ALL in this age group, the therapeutic focus in elderly patients has been on reducing the intensity of chemotherapy. Studies examining induction therapy with imatinib as a single agent or in combination with a low-intensity schedule (vincristine and dexamethasone) in elderly patients have shown excellent initial efficacy with less morbidity and mortality than regimens using more intensive chemotherapy regimens, but relapse remains a serious and frequent clinical problem.^{1–3} Therefore, it is recommended to propose allogeneic stem cell transplantation (SCT) to all eligible patients with a suitable donor.

Among the second-generation TKIs, dasatinib has been the most frequently examined drug in newly diagnosed Ph + ALL, both alone and in combination with different chemotherapy regimens. To date, no randomized comparison between dasatinib and imatinib is available, and follow-up in most dasatinib-based trials is still short.^{4–6} Overall, the efficacy is excellent in terms of complete remission rates, and molecular responses may be superior to imatinib-based regimens, but to date no

standardized comparison of minimal residual disease levels has been performed.

Promising data on remission duration and disease-free survival have been reported, but relapse remains the most frequent cause of treatment failure. It is thus unclear whether or to what degree dasatinib will reduce the relapse rate, as resistance attributed to the T315I gatekeeper mutation of the Bcr-Abl tyrosine kinase domain has emerged as the major limitation of dasatinib in Ph + ALL.^{5,6} Accordingly, allogeneic SCT is recommended as treatment of choice for all suitable patients, even if they have achieved a good molecular response with the more potent second-generation TKIs. Studies incorporating nilotinib and the third-generation TKI ponatinib are ongoing.

ALLOGENEIC SCT

Maintaining the remissions achieved by TKI-based therapy has become the major challenge in treating Ph + ALL, and different approaches are being used depending on the group of patients considered. The probability of patients undergoing allogeneic SCT in first CR has increased with the higher response and lower relapse rates achieved with TKI-based treatment. Allogeneic SCT is the only therapeutic modality convincingly shown to have curative potential.⁷ At present, SCT should be attempted in all patients with a compatible donor who are considered eligible for a transplant procedure. Results with matched sibling and unrelated donors are essentially identical; myeloablative conditioning is the procedure of choice outside of clinical trials. The role of reduced-intensity conditioning, for example, in elderly patients is of interest in view of the transplant-related mortality in these patients, but remains to be determined. In addition, post-transplant strategies are important to reduce the relapse rate.

MAINTENANCE THERAPY

There is no generally accepted type of maintenance therapy in patients not eligible for allogeneic SCT. Usually, imatinib is given either alone or in combination with classical ALL maintenance such as low-dose methotrexate and 6-mercaptopurine. More recent studies use second-generation TKIs, but their long-term efficacy is unclear. An interesting approach in which imatinib is given concurrently with standard or pegylated interferon is currently being tested in clinical studies conducted by the GMALL and GRAALL study groups.^{8,9} Longer follow-up is needed to determine whether this strategy will translate into better relapse-free survival.

MINIMAL RESIDUAL DISEASE ASSESSMENT

Molecular monitoring of minimal residual disease (MRD) during treatment has become a major tool to assess the outcome and to evaluate the risk of impending relapse in childhood and adult ALL. The levels of MRD in the BM of patients with Ph + ALL, assessed with quantitative real-time PCR after induction and after consolidation treatment, are powerful indicators of prognosis.¹⁰ These molecular studies indicate that adult Ph + ALL patients have a heterogeneous sensitivity to treatment, and that early quantification of residual disease may be used for making treatment decisions.

There is compelling evidence that the appearance of Bcr-Abl transcripts is associated with a high risk of relapse after allogeneic SCT. Typically, the median time interval from first positive PCR assay to relapse is short, suggesting the need for timely therapeutic intervention. Discontinuation of immunosuppressive therapy for GvHD prophylaxis and donor lymphocyte infusions have shown little efficacy in ALL. Administration of imatinib appears to be able to reduce the probability of molecular and hematologic relapse if started early after SCT, that is, in the setting of a low leukemic cell burden.¹¹ A current randomized study is exploring the efficacy and tolerability of different interventional strategies consisting of prophylactic or preemptive imatinib administration.

RESISTANCE MECHANISMS

Ph + ALL blast cells are genetically highly unstable and contain acquired genetic abnormalities, which provide insights into pathogenesis and strongly influence prognosis.¹² Overexpression of the *BCR-ABL* fusion gene, due to double Ph + chromosome, activates a number of downstream signaling pathways involving Ras/Raf/mitogen-activated protein kinase and Jak-STAT (Janus kinase signal transducer and transcription activator of transcription).¹³ Development of growth-factor-independent malignant clones contributes to disease progression. Most importantly, relapse is commonly associated with a BCR-ABL kinase domain point mutation that renders the BCR-ABL enzyme insensitive to the drug. Approximately 80% of patients with Ph + ALL who relapse while on imatinib are found to have Bcr-Abl mutations, with predominance of P-loop and T315I mutations.^{14,15} With dasatinib, relapse is by far most frequently associated with the T315I mutation; P-loop mutations are less common. It has become of central interest whether mutations are already present in TKI-naïve patients, and this frequently appears to be the case, as low-level TKD mutations are detected in up to 40% of pretherapeutic leukemic samples of Ph + ALL patients.^{16,17} Thus, mutations may arise randomly, with some of them conferring a growth advantage under the selective pressure of TKIs. The importance of mutations in clinical resistance to available TKI has promoted the search for novel inhibitors, active particularly against the T315I gatekeeper mutation. In addition, a variety of additional, still poorly characterized, mechanisms of non-mutational resistance to TKIs have been suggested.

SALVAGE TREATMENT

As point mutations are the major mechanism of resistance to firstline imatinib therapy in Ph + leukemia, different drugs active on mutant Bcr-Abl or on its signal transduction pathway have been developed and are undergoing clinical testing. Novel TKIs such as ponatinib have demonstrated anti-leukemic activity toward cells expressing a wide variety of BCR-ABL-resistant mutants, including many P-loop mutants, the dasatinib-resistant mutant F317L and the T315I gatekeeper mutant.^{18,19} However, preliminary data from phase I and II studies suggest limited, mostly short-term, clinical efficacy in leukemias that have demonstrated their ability to evade inhibition by first- and second-generation TKIs.^{19,20} This highlights the need for non-ABL-directed therapies for patients with relapsed or refractory Ph + ALL. Interesting immunologic approaches are based on recently developed bispecific T-cell-engager antibodies that transiently engage cytotoxic T cells for lysis of selected target cells. The bispecific antibody construct called blinatumomab links T cells with CD19-expressing target cells, resulting in a nonrestricted cytotoxic T-cell response and T-cell activation. Preliminary results indicate that treatment with blinatumomab is able to convert MRD-positive ALL into an MRD-negative status, and that this is generally well tolerated.²¹

FUTURE TREATMENT CONCEPTS

Other novel compounds that target signaling pathways implicated in promoting leukemic growth and viability or leukemic stem cell self-renewal include inhibitors of the PI3-kinase/AKT/mTOR pathway and the hedgehog pathway, respectively. Development of such novel drugs, in conjunction with optimization of molecular techniques for better quantification of minimal residual disease and identification of resistance mechanisms, will enable the design of trials in which treatment decisions are increasingly based on individualized molecular markers of disease.

CONFLICT OF INTEREST

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