Chronic myelogenous leukemia (CML) is a clonal disorder of hematopoietic stem cells characterized by the Philadelphia (Ph) chromosome (39). Ph chromosome was the first chromosomal abnormality associated with a specific malignant disease in humans, namely CML. Later it was further characterized as a reciprocal translocation between chromosomes 9 and 22 referred to as t (9; 22) (q 34; q 11) (44). The translocation results in the formation of two hybrid genes, BCR-ABL on the Ph chromosome and ABL-BCR on 9q+. The BCR-ABL fusion gene encodes a 210 kDa cytoplasmic protein (p 210BCR-ABL) with elevated tyrosine kinase activity (31) which is regarded as essential to the mechanism that underlies the chronic phase of CML. More than 95 % of patients with CML have a BCR-ABL gene in their leukemia cells. However it is not exclusive to CML because it is found in 10 % to 20 % of adults and in 2 to 5 % of children with acute lymphoblastic leukemia (15, 38). Detection of major BCR-ABL expression at a very low level was also found in blood cells of some healthy individuals (1). BCR-ABL gene has been shown to be a leukemia specific oncogene which activates various transduction pathways leading to proliferation, transformation, loss of adhesive properties, decreased apoptosis and genetic instability (14). Since the tyrosine kinase is constitutively active, the cells bypass regulated growth and undergo a malignant transformation (11). The oncogenic character of BCR-ABL was also confirmed by induction of chronic myelogenous leukemia in mice by the Ph 210 bcr/abl gene (5, 29). CML encompasses three distinct phases becoming more resistant to treatment in each successive phase. The chronic phase is characterized by expansion of terminally differentiated neutrophils. Within 3 to 5 years the disease progresses to an accelerated phase manifested by increasing constitutional symptoms, progressive splenomegaly, refractoriness to standard therapy, rising percentage of blasts without meeting the criteria for acute leukemia. The duration of the accelerated phase may last as long as one year. The terminal acute phase termed blast crisis is characterized by cells that fail to mature and represent undifferentiated myeloid or lymphoid progenitor cells. The BCR-ABL oncogene is present in all stages. The blast crisis is characterized by additional genetic abnormalities (18).

Therapy of CML

CML can be cured only by hematopoietic stem cell transplantation. Allogeneic bone marrow transplantation is largely limited to younger patients with an HLA-identical sibling in an acceptable health status to tolerate the procedure. Stem cell transplantation should preferably be offered to patients within 1 year of diagnosis. For all other patients chemotherapy was the only therapeutic option. For many years the principal options for treating CML included busulphan and hydroxyurea. Busulphan demonstrated a 90% hematologic response, but did not alter the progression of the disease. The survival outcome was 3 to 4 years. Hydroxy-
urea induced to the therapy several years later had a longer duration in chronic phase, but the progression to blast crises was not deterred. The median survival was 4 to 5 years (53). After introduction of interferon – α (IFN – α) in the mid 1980 (50) in the therapy of CML the survival compared with hydroxyurea was prolonged. IFN – α induced in 80 % of patients in chronic phase CML a complete hematologic remission and in 26 % patients complete cytogenetic remission (25). The addition of ARA-C to IFN further improved survival but increased toxicity (9).

Novel therapies for CML were pursued and various signal transduction inhibitor were developed, among them STI-571 (imatinib mesylate, Gleevec, Glenvec) a 2-phenylaminopyrimidine. Imatinib is a highly selective inhibitor of the protein tyrosine kinase family, which includes BCR-ABL protein, the platelet-derived growth factor (PDGF) receptor and the c-kit receptor (12, 45). Imatinib competitively binds to the ATP-binding site of BCR-ABL and inhibits protein tyrosine phosphorylation (47). In vivo studies STI-571 prevented growth of hematopoietic cells that expressed BCR-ABL but did not affect normal cells and their function (11).

**Imatinib in the late chronic phase CML**

On the basis of the promising preclinical data, in June 1998 Drucker at al (13) initiated a phase I trial designed to determine the safety and efficiency. The efficiency was found to be with the dose over 300 mg/day. 54 patients in the late chronic phase CML who were unable to tolerate IFN – α or who had no response to the drug were enrolled in the study.

The criteria for response to IFN – α were as follows (49):

- **CHR** (complete hematologic response): normalization of peripheral counts and differential count, disappearance of all signs and symptoms of disease
- **PHR** (partial hematologic response): similar to CHR except for persistence of peripheral immature cells (blasts, promyelocytes, myelocytes), persistence but improvement more than 50 % in splenomegaly.
- **CR** (cytogenetic responses)
  - complete: no evidence of Ph-chromosome positive cells
  - major: Ph 1–35 %
  - minor: Ph 36–65 %
  - minimal: Ph 66–95 %

Out of 54 patients 53 (98 %) achieved CHR and 17 (31 %) major cytogenetic responses. Normal leukocyte and platelet counts were reached usually within four weeks after the initiation of treatment.

Good effect of imatinib therapy was also confirmed in further studies in patients with late chronic phase CML in whom previous therapy with IFN – α failed. In phase II trial a total of 454 patients were treated with 400 mg of oral imatinib daily. Imatinib induced CHR in 95 % of patients, major cytogenetic response in 60 % and 41 % of the total number of patients experienced complete cytogenetic remission. Progression-free survival was 89 % at 18 months (24).

Voglová et al. (54) used the same dose 400 mg of imatinib daily in 34 patients with late chronic phase CML in whom IFN – α failed. Complete hematologic response was achieved in 33 of 34 (97 %) patients, complete plus major in 21 (63 %) patients. The median follow-up time was 97.5 weeks (23–115). Cytogenetic relapse was observed in 2 of 33 patients (6 %), additional cytogenetic abnormalities in 4 (12 %) patients.

**Imatinib as the frontline therapy in CML**

The positive results with imatinib in the late chronic phase CML were followed with the phase III trial in which 1106 patients were randomized to the two arms. Imatinib was used as frontline therapy in 553 patients and the results compared with the same number of patients treated with IFN – α plus ARA-C. Complete cytogenetic remission was achieved in 68 % of patients (vs 7 % in IFN – α plus ARA-C arm). Imatinib was found to have longer time to progression. The results of this study suggest that imatinib should be utilized as frontline therapy in CML (9).

Hematologic responses with imatinib typically occur within 3 months, major cytogenetic responses after 9–12 months of therapy.

The trials with imatinib in late chronic phase or as frontline therapy in CML have shown remarkable results. Imatinib is superior to IFN – α and ARA-C in terms of cytogenetic response, progression rates, tolerability and quality of life. The durability of response, the possible long-term effect and the survival data are unknown. Imatinib is used since June 1998, that means 5 years, the median survival with combination of IFN – α plus hydroxyurea was 89 months (25). It can be only supposed that the survival will be better because of high complete cytogenetic responses as compared with IFN – α.

**Imatinib in accelerated phase CML**

In accelerated phase CML, phase II trial showed that patients taking 600 mg/d imatinib had longer time to progression and superior survival when compared to 400 mg/d. With the two different dosage regimens cytogenetic response with 600 mg/d was 28 % vs 16 % and survival at 12 months 78 % vs 65 %. In 181 evaluated patients the overall hematologic response was 82 % with 34 % CHR. Major cytogenetic response was 24 %, complete cytogenetic response 17 %. There was no higher toxicity with the 600 mg oral dose (51).

**Imatinib in blastic phase CML**

In CML blast crises, two recently published studies showed benefit in using imatinib over standard cytotoxic
Imatinib for relapse after allogeneic stem cell transplantation for chronic myelogenous leukemia

Relapse after allogenic SCT has been treated with donor lymphocyte infusion (DLI), IFN – α therapy, or additional transplantation. Although DLI can produce complete molecular-level response (ie abolishment of the BCR-ABL oncoprotein), it can also cause recurrence of GVHD, myelosuppression-associated complications, and death (30). IFN – α based therapy is only moderately successful, second transplantation is usually reserved for patients whose disease does not respond to DLI.

Imatinib mesylate (400 mg - 1000 mg) was used in 28 adults with CML that had relapsed after allogenic SCT (22). Thirteen patients had undergone salvage donor lymphocyte infusion. CHR rate was 74 % (17 of 23 patients) and the cytogenetic response rate was 58 % (15 of 28 patients). The 1-year estimated survival rate was 74 %, complete response in 9 (35 %) patients CHR rates were 100 % for chronic phase, 83 % for accelerated phase and 43 % for blastic phase. Recurrence of GVHD occurred in 5 patients (in 3 grade 3), severe granulocytopenia in 43 % and thrombocytopenia in 27 %. Imatinib effectively controlled CML that recurred after allogenic SCT but was associated with considerable side effects. Imatinib therapy alone may be reasonable especially in patients who still have persistent GVHD at the time of CML recurrence to avoid potential worsening of GVHD (22).

Imatinib mesylate dosage

Imatinib is used in standard doses of 400 mg/day for patients in chronic phase, 600 mg/day for patients in accelerated phase and up to 1000 mg in blastic phase. Kantarjian et al. (26) on the basis of positive current clinical experience and the experience with higher doses of imatinib (600 mg) in accelerated phase recommended the investigation of higher dose as frontline therapy in patients with newly diagnosed or in late chronic phase CML to obtain better and more durable complete cytogenetic and possibly molecular remission. Dose adjustment is often necessary due to side effects. When serious hematologic toxicity or non-hematologic adverse effects develop it is usually necessary to stop imatinib and to restart at a lower dose after the toxicity resolved.

Monitoring the response to therapy

For patients in chronic phase cytogenetic response can occur within 3 months of starting therapy. Marrow assessment with metaphase cytogenetics (fluorescence in situ hybridization) can be used after six months for this purpose. Patients in major cytogenetic remission should be optimally monitored by quantitative real-time reverse transcriptase polymerase chain reaction (RT-PCR) for the presence of BCR-ABL transcripts. It is important to continue to perform conventional cytogenetics at regular internal to detect additional chromosomal abnormalities.

Myelosuppression

In the chronic phase the current policy is to interrupt imatinib at the first episode of grade III-IV neutropenia/or thrombocytopenia. Treatment can be resumed once the absolute neutrophil count has risen above 1 x 10⁹/l and/or the platelet count above 100 x 10⁹/l. If the blood counts fails to recover within two weeks, it is recommended to reintroduce imatinib at the lower dosage of 300 mg (36).

In patients in blastic phase the support with red cells, platelet transfusions and G-CSF is usually necessary.

The non-hematologic side effects (36, 54)

Increase of weight and peripheral edema occur in about 60 % of patients. Common are muscle craps, bone pain and weight gain. Others include nausea, vomiting, diarrhea, constipation, dizziness, fatigue, headache, and acne. Severe side effects are uncommon, and include fever, neutropenia (< 0.5 x 10⁹/l) and thrombocytopenia (< 10 x 10⁹/l) occurred in 54 % of patients with ALL. Imatinib therapy resulted in a clinically relevant hematologic response rate in relapsed or refractory Ph+ ALL patients, but development of resistance and subsequent disease progression were rapid, but the clinically relevant response offers the possibility of SCT.
arthralgias. Normally the patients respond well to non-steroidal anti-inflammatory drugs. Relatively common are skin rashes. They usually appear soon after commencing imatinib therapy, but may develop several weeks or even months later. Hsiiao et al. reported a patient in blast crisis who developed a life-threatening cutaneous reaction, Stevens-Johnson syndrome, following 1 week of mesylate therapy (20). Hepatotoxicity grade II – IV has been reported in 2–15 % (36, 54). It typically presents as mild hepatitis, but a cholestatic pattern has been also seen. Other less frequent non-hematologic side effects include fatigue, weakness, dyspepsia, pyrexia, anorexia, hypokaliemia. Increase of intraocular pressure was also noticed in one patient (54).

Resistance of CML to imatinib mesylate

Imatinib demonstrated remarkable activity in CML but a critical clinical problem is the resistance to this compound. The estimated 2 year incidence of imatinib resistance was 10 % in the chronic phase and 40 % to 50 % in accelerated phase post interferon – α failure (26).

The relative resistance of blast phase to imatinib was considered to be consistent with the hypothesis that secondary mutations (and not BCR-ABL itself) are responsible for the resistance. Nevertheless Deininger et al. (6) made the observation that some cells do escape to the pro-apoptotic effect of mesylate and are able to establish a subline of cells that can grow continuously in the presence of pharmacologic concentrations of imatinib that inhibit growth of most other CML lines. It has also been observed that some quiescent CD 34+Ph cells were highly insensitive to imatinib (19). A variety of mechanisms involved in imatinib resistance to CML have been described (17, 32). They include BCR-ABL amplifications (an extra Ph chromosome or high level of BCR-ABL mRNA for other reasons) (55), or mutations within the protein kinase domain (3). Up till now at least 9 different point mutations have been identified (33). There is currently little insight into the underlying mechanism that leads to BCR-ABL gene amplification or mutation. It has been suggested that BCR-ABL itself may confer a mutant phenotype leading to greater genetic instability during disease progression. Some data lead one to believe, that clinical resistance to imatinib, just like antibiotic resistance to bacteria, arises through a process by which pre-existing mutant cells outgrow drug sensitive cells (34). It has been recently confirmed that BCR-ABL mutations preexist in patients who had never received imatinib (16). Further mechanisms of resistance are increased levels of plasma α – 1 acid glycoprotein (16), that binds to imatinib in the serum and blocks its activity against BCR-ABL, overexpression of Pgp multidrug resistant protein, that may impair the uptake of imatinib by resistant subtype (35), some other tyrosine kinases (7), enhanced expression of the interleukin 3 which protects BCR-ABL transformed hematopoietic progenitor cells from apoptosis induced by BCR-ABL tyrosine kinase inhibitors (10).

A critical clinical question is how to overcome or circumvent the resistance. The escalation of the dosage is successful in some cases but not in other (4, 26). It has been observed, that patients who have become resistant to the drug responded again if imatinib has been temporarily interrupted (52). Most promising approach is the combination of imatinib with other treatment modalities such as immunotherapy with specific vaccines (42), interferon, convention chemotherapy (ARA-C) (37) which are now being examined. Other possibilities are to combine various signal transduction pathway inhibitors (8, 48). One might exploit drugs that trigger BCR-ABL protein degradation such as geldamycin or 17-AGG (2). A number of novel agent are still under investigation for treatment of CML.

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