Imatinib mesylate in children and adolescents with cancer

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Abstract

Imatinib is an inhibitor of the *BCR-ABL* fusion gene product that characterizes chronic myeloid leukemia (CML), and of the related tyrosine kinases c-KIT and platelet-derived growth factor (PDGF) receptor. The drug is now included as front-line therapy for CML and Philadelphia chromosome-positive acute lymphoblastic leukemia in children and adolescents, though valid concerns about serious late sequelae remain unresolved and are important issues for further study. European and North American consortia have conducted phase I and II clinical trials of imatinib in children and adolescents with brain and other solid tumors that have provided little evidence of efficacy.
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Introduction

Imatinib mesylate (imatinib, STI 571) is a low molecular weight, synthetic, 2-phenylaminopyridine derivative that was developed as a selective inhibitor of the BCR-ABL fusion gene product, a tyrosine kinase, that results from the balanced translocation [t (9; 22) (q34; q11)] between the long arms of chromosomes 9 and 22 that is manifest cytogenetically as the Philadelphia (Ph) chromosome. The Ph chromosome occurs in a small minority of children with acute lymphoblastic leukemia (ALL), but in about 1/3 of adults with this disease\(^1\). Chronic myeloid leukemia (CML) accounts for less than 2% and ALL approximately 80% of leukemias in children\(^2\); and ALL is the commonest form of malignant disease (25-30% of cases) in this age group\(^3\).

When the translocation involves the major breakpoint cluster region, BCR-ABL encodes a 210 kilodalton (kD) dysregulated tyrosine kinase which is a hallmark of the great majority of cases of CML in both adults and children\(^4\). Imatinib competes for the ATP binding site of the kinase and so inhibits the tyrosine phosphorylation of proteins involved in BCR-ABL related signal transduction\(^5\). Translocations involving the minor breakpoint cluster region lead to the production of a 190 xDa protein that occurs in 80-90% of Ph + ALL in children.

Imatinib is marketed as Gleevec\(^\text{\textregistered}\) in North America and Glivec\(^\text{\textregistered}\) in Europe by Novartis Pharmaceuticals and is available as 100mg and 400mg capsules. In vitro data demonstrate that the contents of the capsule can be dissolved and remain stable in water and apple juice but not in orange juice, cola or milk\(^6\). The drug is well-absorbed after oral administration with bioavailability approximating 100% in healthy volunteers\(^7,8\). It is extensively bound to plasma proteins, notably alpha 1 acid glycoprotein, and is metabolized to the active form (CGP74588) mainly by the hepatic cytochrome P450 enzyme system\(^9\). There are several accounts of pharmacokinetic, pharmacodynamic and pharmacogenetic studies of imatinib in children\(^6,9-12\). The notable variation between patients may reflect the wide spectrum of activity (4-5 fold) in the general population of CYP3A\(^13\), a key enzyme system responsible for the biotransformation of imatinib.

Spectrum of activity

The use of imatinib in diseases other than those characterized by BCR-ABL expression is based on the biology of other Type III receptor tyrosine kinases, notably c-KIT (CD117) and platelet-derived growth factor (PDGF) receptors which are structurally and functionally closely related\(^14,15\). On binding their respective ligands - stem cell factor and PDGF - these receptors have an important role in signal transduction that results in cell survival. This process of signal transduction is inhibited by imatinib in a fashion similar to its effects on the BCR-ABL transcribed protein\(^16,17\), leading to selective inhibition of proliferation and induction of apoptosis\(^5\). It appears that imatinib does not affect other closely related protein kinases\(^18,19\).
In children and adolescents c-KIT is expressed by some tumors, including a variable proportion of osteosarcoma\(^{20}\), Ewing sarcoma\(^{20,21}\), synovial sarcoma\(^{20,22}\), neuroblastoma\(^{20,23}\), malignant germ cell tumors (including intra-cranial germinomas\(^{24}\)), and gastro-intestinal stromal tumors (GIST)\(^{25}\) as well as Epstein-Barr virus positive nasopharyngeal carcinoma\(^{26}\) and core-binding factor acute myeloid leukemia (CBF-AML)\(^{27}\). Such expression is an indication that the tumor cells depend on this pathway for survival.

Likewise, PDGF and its receptors are expressed in pediatric tumor samples and cell lines from osteosarcoma\(^{28-30}\), synovial cell sarcoma\(^{22,31}\) and desmoplastic small round cell tumor\(^{20,32-34}\). PDGF is also expressed in more than 80% of malignant gliomas\(^{35}\) and its beta receptor in more than 90% of dermatofibrosarcoma protuberans\(^{36}\).

**Pre-clinical studies**

Imatinib has activity against Ewing sarcoma\(^{37,38}\) and neuroblastoma\(^{39}\) cell lines in vitro as well as in xenograft models of these tumors\(^{37,39}\), at drug concentrations achievable in humans in vivo. Similarly, imatinib can inhibit the result of c-KIT exon 8 mutations in CBF-AML in vitro\(^{27}\). By contrast, the drug inhibited PDGF intracellular signal transduction in osteosarcoma cell cultures only at supra-therapeutic concentrations\(^{30}\).

**Evidence from clinical experience**

Imatinib is now the first-line therapy for all phases of CML and GIST\(^{40}\) in adults but is approved for use in children only in CML\(^{12}\). As a consequence of the low incidence and prevalence of these disorders in children and adolescents, the level of evidence for the efficacy of imatinib in these diseases, and in others, is variable.

1. Chronic myeloid leukemia - the biology of CML in adults and younger subjects is very similar, hence the case for the approved use of this drug in children with this disease\(^{12}\). The evidence for efficacy in adults is overwhelming\(^{40-44}\), including a phase III trial in more than 1000 patients with newly diagnosed chronic phase disease in which imatinib was demonstrated to be superior to the first line therapy with interferon and low dose cytosine arabinoside\(^{40}\). This trial enrolled subjects > 18 years of age and the main outcome measures, all of which favored imatinib, were hematologic and cytogenetic remission and freedom from progression of disease. Imatinib is active in the accelerated phase of CML\(^{44}\) as well as in blast crisis and Ph chromosome-positive ALL\(^{42}\). The drug is also efficacious in chronic eosinophilic leukemia with all 33 patients achieving a complete hematologic remission in less than 1 month in a recent study\(^{45}\). This disease is characterized by an interstitial deletion of the long arm of chromosome 4 leading to a fusion gene coding for a constitutively activated form of PDGF receptor alpha\(^{45}\). Two children with this disorder have been reported\(^{46}\).

As determined by randomised phase III trials by both French\(^{47}\) and German\(^{48}\) CML study groups, doses of imatinib higher than the standard 400 mgs/day, with or without interferon, resulted in more rapid attainment of molecular remission. However, at least in short-term follow-up, this has not resulted in better overall or progression-free survival\(^{48}\). It appears that complete molecular remission can be sustained for 3-4 years after discontinuation of
imatinib, although experience to date is limited to 8 patients\textsuperscript{49}.

While the adherence to imatinib therapy is clearly critical\textsuperscript{50}, resistance to the drug is also an important determinant of responsiveness. Some BCR/ABL mutants can be overcome by higher-doses of imatinib and some by second line agents (dasatinib and nilotinib)\textsuperscript{51} which can be useful in patients who are intolerant of imatinib\textsuperscript{52}. Responsiveness to second-line agents is related to second generation inhibitor (SGI) clinically relevant mutants\textsuperscript{53}. Emerging options for those who are resistant to two or more tyrosine kinase inhibitors, often mediated by the T315I BCR/ABL mutation, include omacetaxine that was demonstrated to have at least short-term efficacy in a multi-centre phase II/III study\textsuperscript{54}. Of the 30 patients in chronic phase, 18 achieved complete hematologic remission, 6 cytogenetic remission and 3 molecular remission. Assessments of the value of dasatinib and nilotinib before\textsuperscript{55} and after\textsuperscript{56} allogeneic stem cell transplantation have been undertaken, but the results are as yet preliminary. However, it does appear that both dasatinib\textsuperscript{57} and nilotinib\textsuperscript{58} are more efficacious than imatinib as first line therapy in patients with chronic phase disease.

In the pre-imatinib era, the Berlin-Frankfurt-Muenster (BFM) consortium enrolled 200 children and adolescents, over a period of a decade, in a trial of allogeneic stem cell transplantation for CML\textsuperscript{59}. The great majority, 85\%, were in chronic phase. For those with matched sibling donors the overall survival at 5 years was 87\% ± 11\%. In their second trial they enrolled 51 patients in a prospective study of imatinib\textsuperscript{60}. With a median follow-up of 19 months, all 47 patients with chronic phase disease are alive. As only about 50 children are diagnosed with CML each year in the USA, there is no prospect of a phase III clinical trial of imatinib in this age group in North America\textsuperscript{61}. The same challenge exists in Europe, although an international study is a possibility.

The Children's Oncology Group (COG) undertook a phase 1 study of imatinib in 31 subjects less than 22 years of age from 23 centres\textsuperscript{6}. The study sample consisted of 14 patients in chronic phase CML, 7 with advanced myeloid leukemias (one AML and 6 blast crisis CML) and 10 with advanced lymphoid leukemias. Entry criteria included refractory or recurrent Ph + disease. Adverse events were graded according to the Common Toxicity Criteria Version 2.0 for Toxicity and Performance Reporting from the National Cancer Institute (NCI/CTC criteria)\textsuperscript{62}. There were 479 total courses (28 consecutive days) of imatinib in doses of 260-570 mg per m\textsuperscript{2} per day and the frequency of non-hematologic adverse events is given in Table I. The great majority were grade 1 or 2, although the occasional occurrence of considerable fluid retention has been reported by others\textsuperscript{63}. No effort was made to define a maximum tolerated dose because of the high response rate at doses of imatinib comparable to or greater than those used routinely in adults: all patients (n=14) with chronic phase CML had complete hematologic responses and 83\% (12/14) had a cytogenetic complete remission.

A consortium of 23 centres in 8 European countries enrolled 30 children and adolescents (age 1-17.5 years) with CML in a phase II study\textsuperscript{64}. The subjects received imatinib at 260-340 mg per m\textsuperscript{2} per day for periods ranging from 1-38 months (on average more than 2 years). In those with chronic phase disease a complete hematologic response was achieved in 80\%, while remission on cytogenetic and molecular genetic criteria was accomplished in 60\% and 50\% respectively. No patient in accelerated phase or blast crisis attained a molecular
remission but 6/8 a complete hematologic response. The frequency of non-hematologic adverse events, using the NCI/CTC criteria, is displayed in Table II. The higher proportions than in the COG phase I study likely reflect the much longer exposure to imatinib. The availability of imatinib clearly has had a marked impact on the treatment of CML in children and adolescents.61

2. Ph positive acute lymphoblastic leukemia

In October 2009 the first detailed report of the COG study AALL 0031 was published.65 Imatinib was given with intensive chemotherapy to all patients and administered for 6 months following transplantation in those (the minority) who underwent this procedure. The 3 year event-free survival was approximately 80 per cent – roughly double that in historical controls – in the group who received continuous imatinib for more than 1 year (cohort 5). The drug was well-tolerated, both before and after transplantation, and survival was no better in the transplanted patients. Although the longest follow-up is only about 5 years from diagnosis, so far no relapses have been reported among those who completed therapy; an issue of importance in the context of the theoretical reduction of a graft-versus-leukemia effect as a consequence of imatinib-induced inhibition of T lymphocyte function,66 although BCR-ABL specific cytotoxic T cells have been described as emerging in the bone marrow of patients with Ph+ ALL during long-term therapy with imatinib.67 With longer follow-up and analyses limited to those who were in cohort 5, outcomes remain excellent.68

A consortium of European groups opened the EsPhALL study in 2004. This was a randomised trial to evaluate the efficacy of imatinib after remission induction, with continuing chemotherapy delivered according to a BFM backbone, in good risk patients, who accounted for 65-70% of the total with Ph+ ALL, defined by early response to chemotherapy. The trial was amended in late 2009 in response to the publication of the finding of COG AALL0031 so that all patients, independent of risk category, received imatinib in an open label phase II study design (Biondi A, personal communication). As patients will still have the option to proceed to hematopoietic stem cell transplantation, this will afford an important comparison with the COG trial.

The report from COG does not address graft-versus-host disease (GVHD); an important consideration given the apparent efficacy of imatinib, albeit with appreciable toxicity, in ameliorating chronic GVHD.69,70 There is an obvious need to undertake phase III clinical trials in GVHD, as well as to assess the value of dasatinib and nilotinib which are more potent inhibitors of BCR-ABL kinase.71,72 The former is to be used in the next COG study (AALL0622) because of additional inhibition of SRC73, though this drug is associated with notable frequency, 35% of pleural effusions.74 Dasatinib will be integrated early (day 15) rather than at the end of induction as was done with imatinib in AALL0331 (Hunger S, personal communication).

3. Gastrointestinal stromal tumors (GIST) – these tumors appear to arise from the interstitial cells of Cajal (ICC), the so-called “pacemaker” cells of the gastro-intestinal tract.75,76 In the great majority of cases GIST express c-KIT or PDGF receptor alpha as do ICC.77,79

Unlike CML, GIST in children is very different from GIST in adults. The tumors in children
show a striking predominance in females, are more often metastatic, may occur as part of the Carney triad (GIST, pulmonary chondroma and extra-adrenal paraganglioma) and reveal an epithelioid rather than a spindle-like morphology.

GIST in children usually express wild-type c-KIT and PDGF receptor alpha, in contrast to the tumors in adults that typically show gain-of-function mutations. Tumors with wild-type expression of c-KIT in adults show a much lower response rate to imatinib that do those with the common exon 11 mutation (44.6% versus 71.7% in one study) suggesting that the tumors in children may be relatively resistant to imatinib.

The decidedly limited clinical experience in the use of imatinib in children and adolescents with GIST reflects the rarity of this disorder in this age group. For example, in 276 patients with non-rhabdomyosarcoma soft tissue sarcoma treated at St. Jude Children’s Research Hospital over 40 years, only 7 had a GIST; at Memorial Sloan Kettering Cancer (MSKCC) there were 350 patients with GIST in a period of 20 years and more, and only 5 were children; while in the archives of the Armed Forces Institute of Pathology there are records of 1782 cases of GIST in approximately 27 years and 44 of them were less than 21 years of age.

Relative refractoriness to imatinib was evident in 6 children with metastatic disease who were treated at MSKCC for periods of 3-18 months. One had stable disease, 4 showed no response and 1 exhibited improvement at some sites and progression at others.

The Intergroup phase III clinical trial that accrued 746 patients at 148 centres in the US did enroll patients as young as 18 years of age but the outcome in the subgroup of adolescents was not analyzed separately. The report of an even larger European study, with 934 evaluable subjects, was similarly uninformative with respect to younger patients.

However, another inhibitor of tyrosine kinase receptors – sunitinib malate – is 10 times more potent than imatinib with respect to inhibition of wild type c-KIT. Reports on a total of 11 children who had been treated previously with imatinib indicate that 2 patients had a response, 6 stable disease, 1 progressed and 2 were intolerant of the drug. The COG has started a phase I trial of sunitinib.

4. Other clinical trials of imatinib in children and adolescents

a. The Pediatric Brain Tumor Consortium has undertaken a phase I study of imatinib in 84 patients aged 3-21 years with newly diagnosed brainstem gliomas or recurrent malignant gliomas. The objective was to determine the maximum tolerated dose in the context of radiotherapy, and was based on the prior observation of expression of PDGF or its receptors in a high proportion of malignant gliomas and the potential for imatinib to contribute radiosensitization. Concern was expressed about the frequency of occurrence of intratumoral hemorrhage (more than 10%), although the investigators noted that this is a well-recognized complication of irradiation alone. One patient developed renal insufficiency. Although a maximum tolerated dose was not identified, it was recommended that the dose of imatinib in a phase III trial in this setting should be 265 mg per m² per day.
A Canadian pediatric brain tumor consortium\textsuperscript{80} enrolled 19 patients, aged 2-18 years, with recurrent or refractory CNS tumors, with or without lepto-meningeal spread (two strata) in a phase II trial of imatinib. Radiotherapy had been given to all but one patient. For inclusion the tumors had to express PDGF receptor alpha or c-KIT, that were detected by immunohistochemistry in 100% and 58% of cases respectively. Imatinib was administered at 440 mg/m\textsuperscript{2}/day for 28 days per course. The median number of courses received was one, maximum 26, total 70. In general the drug was well tolerated with few interruptions or dose reductions, but hematological toxicity was common and gastro-intestinal side effects were reported with slightly less frequency. No patients developed intra-tumoral bleeding. Four patients had stable disease for 38, 38, 39 and 104 weeks, the last receiving 26 courses, but all eventually progressed. All 4 patients had tumors expressing c-KIT and none had lepto-meningeal disease. The remaining patients all progressed within 16 weeks. The authors speculated that the poor responses to imatinib may have reflected the low penetration of the blood-brain barrier by this drug; a position supported by their finding of CSF levels less than 5% of the corresponding plasma concentrations, and the studies in adults with AML\textsuperscript{81} and CML\textsuperscript{92}. By contrast, based on direct contrast in a pre-clinical model, dasatinib crosses the blood-brain barrier much more effectively in such adult patients\textsuperscript{93}.  

b. The COG performed a phase II trial of imatinib in patients less than 30 years of age who were diagnosed with osteosarcoma, Ewing sarcoma, neuroblastoma, desmoplastic small round cell tumor, synovial sarcoma or GIST\textsuperscript{11}. The drug was given in 28 day courses at a dose of 440 mg per m\textsuperscript{2} per day. There were 59 evaluable patients of whom only one, with Ewing sarcoma, had an objective response. Hemorrhagic pleural effusions occurred in 7 patients with pulmonary lesions and an additional 3 patients experienced intra-tumoral bleeding.  

c. A European consortium, including investigators of Innovative Therapies with Children with Cancer (ITCC), enrolled 33 subjects less than 22 years of age who had “solid malignancies” in a phase II trial of imatinib at doses ranging from 340-440 mg per m\textsuperscript{2} per day. The primary purpose of this study was pharmacological and no clinical outcome data were reported\textsuperscript{9}. The ITCC published subsequently\textsuperscript{94} on clinical outcomes in 36 patients with “solid tumors” characterized by immuno-histochemical positively for c-KIT in ≥ 30% of cells or PDGF receptor alpha or beta in ≥ 80% of cells. These patients had progressive, refractory or relapsed disease, including 12 with brain tumors and 15 with an assortment of bone sarcomas and soft tissue tumors. Ten of 32 evaluable patients had stable disease for periods ranging from 5 to more than 42 months. However, included in this group were 3 of 6 patients with fibromatosis, a disorder that is not usually classified as cancer and that often follows an indolent clinical course. In the absence of tumor regression, all patients eventually had progressive disease. Although adverse events were common, including nausea and vomiting in 50% of the patients, these were usually of mild or moderate severity and the drug was generally well tolerated.  

**Additional relevant observations**  

Dermatofibrosarcoma protuberans (DFP). This indolent tumor is characterised by the fusion of the PDGF receptor beta gene on chromosome 22 with the COL1A1 promoter gene on chromosome 17, leading to over-expression of the former. Imatinib has clinical activity in this disorder, as exemplified by the Novartis-sponsored B 2225 multi-centre phase II study\textsuperscript{95}, and there are reports of a small number of children with DFP who were responsive to
imatinib$^{96,97}$. The exhibition of anecdotal activity in the neo-adjuvant setting$^{98}$ offers an attractive prospect in children, with the potential to reduce the extent of surgical resection.

Systemic mastocytosis (SM). In a study of 19 children/adolescents and 48 adults, the presence of urticaria pigmentosa (cutaneous mastocytosis) was associated with SM in adults but not in the younger age group, although SM does occur in children$^{99}$. In adults SM is characterised by the D816V c-KIT mutation$^{100}$, but a phase II clinical trial of imatinib in 20 patients yielded disappointing results, despite administration of a daily dose of 400mg for a median duration of 9 months$^{101}$. An earlier phase II trial in 14 patients, 11 of whom exhibited the D816V mutation, provided evidence of the clinical efficacy of imatinib in SM using the same dose for a shorter average interval$^{102}$. This apparent discrepancy has suggested that responsiveness to imatinib in this disorder may be dependent on the presence of additional imatinib-sensitive c-KIT mutations$^{101}$. The single case report of successful treatment for progressive cutaneous mastocytosis in a young child included identification of a c-KIT mutation, somatic deletion, known to respond to imatinib$^{103}$.

**Long-term effects of imatinib in children**

In the context of a French national phase IV clinical trial of imatinib in chronic phase CML, growth retardation was recorded in a group of 22 children with a median reduction in the height Z score of 0.37 over the first year of treatment$^{104}$. This effect can be dramatic, as exemplified by a child whose height dimished from the 74th centile to the 9th centile over 3 years of treatment with imatinib$^{105}$. Case reports of diminished growth velocity in two children receiving imatinib for at least 4 years$^{106,107}$ prompted a group of Australian investigators to examine the effect of the drug on bone growth in rats. They demonstrated a reduction in the thickness of growth plates through the inhibition of chondrocyte proliferation, perhaps mediated by a reduction in the activity of PDG receptor beta, a known stimulant of chondrocytes$^{108}$. Although the growth velocity recovered in both children following discontinuation of imatinib, it is clearly important to remain alert to the prospect of a negative impact on growth in children who experience prolonged exposure to this drug.

In the anecdotal clinical reports, diminished longitudinal growth was accompanied by reduced bone mineral density, in one case$^{109}$ associated with gynecomastia, an increase in serum follicle-stimulating hormone and a reduction in inhibin B. The authors of that report conjectured that this imbalance may have been the causal mechanism of osteopenia via perturbation of KIT activity. Certainly gynecomastia and altered bone mineral metabolism$^{110}$ have been observed in adults receiving imatinib.

It has been proposed that the biochemical aberration encountered in such adults, notably hypophosphatemia in the majority, with some patients demonstrating elevated blood levels of parathyroid hormone, set the stage for osteomalacia$^{110}$. However, other investigators in Sweden$^{111}$ and Australia$^{112}$, while confirming the common finding of hypophosphatemia, have observed increased cortical bone mineralisation$^{111}$ and trabecular bone volume$^{112}$, suggesting an uncoupling of bone formation and bone resorption in the homeostatic process of bone re-modeling among adult patients with CML who received imatinib. The Australian group have offered an explanation for these findings based on a molecular mechanism related to stimulation of gene expression in pathways known to promote osteogenesis and mineralized matrix production$^{112}$. Exploring similar phenomena in children with Ph+ leukemia who receive imatinib should be a priority, for the treatment of non-Ph+
ALL in childhood is associated with clinically significant bone demineralization in up to 2/3 of patients\(^{113}\). A further challenge is posed by data from the Spanish registry for CML which point to a better hematologic response to imatinib in patients who develop hypophosphatemia\(^{114}\). The subject of dysregulation of bone remodeling by imatinib has been reviewed in detail recently\(^{115}\).

In an international study of the long-term effects of imatinib in more than 900 adults with CML, the most common serious adverse event was “heart failure”\(^{116}\). Studies in vitro and in animals, the latter using enormous doses of imatinib, that is 50-200mg per Kg, have suggested putative mechanisms for drug-induced cardiotoxicity\(^{117}\). Evidently this is a matter of potential concern in children and adolescents with Ph+ ALL, for all of them will receive an anthracycline in addition to imatinib.

**Reported experience in developing countries**

There are few published accounts of the use of imatinib in countries with limited resources, but reports have appeared from Brazil\(^{118}\), Pakistan\(^{119}\), India\(^{120}\), Mexico\(^{121}\) and China\(^{122}\) (Table III). The number of children and adolescents is not provided in any of these accounts, but the overall experience matched that in industrialized societies with respect to hematological, cytogenetic and molecular genetic responses. The somewhat poorer results from India prompted the authors to suggest that pharmacogenomic studies may be informative. Experience in India and China indicated that skin hypo-pigmentation was a common form of toxicity, seldom if ever reported from Western countries. It may be relevant that a generic form of imatinib, from CIPLA in India, is in common use in developing countries.

The issue of cost was raised by the investigators in Brazil, Mexico and China; even limiting access to imatinib. In Mexico it was calculated that the average cost of a non-myeloblastic allogeneic stem cell transplantation (US$18,000) was equivalent to 180 days of therapy with imatinib; an important observation given the fact that allogeneic stem cell transplantation remains a commonly exercised option in CML\(^{123}\). However, the Glivec International Patient Assistance Program (GIPAP), a partnership setup by the manufacturer (Novartis) with several NGOs, has demonstrably improved the access to imatinib of patients with CML in low and middle income countries\(^{124}\).

It is clear that we are on the threshold of a tsunami of targeted therapies for children and adolescents with cancer\(^{125}\), of which imatinib is but an early wave.
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Table I

Frequency of non-hematologic adverse events in the Children's Oncology Group Phase I Study of imatinib in chronic phase chronic myeloid leukemia*

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Frequency (%)</th>
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<tbody>
<tr>
<td>Nausea</td>
<td>4.0</td>
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<tr>
<td>Vomiting</td>
<td>3.5</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3.5</td>
</tr>
<tr>
<td>Increased AST</td>
<td>3.8</td>
</tr>
<tr>
<td>Increase ALT</td>
<td>2.9</td>
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<tr>
<td>Diarrhoea</td>
<td>2.7</td>
</tr>
<tr>
<td>Arthralgia/myalgia</td>
<td>1.5</td>
</tr>
<tr>
<td>Oedema/weight gain</td>
<td>&lt;1</td>
</tr>
</tbody>
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* From reference number 5
### Table II

**Frequency of non-hematologic adverse events in the European Phase II study of imatinib in various clinical phases of chronic myeloid leukemia***

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Frequency (%)</th>
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<tbody>
<tr>
<td>Nausea</td>
<td>13</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10</td>
</tr>
<tr>
<td>Increased AST/ALT</td>
<td>7</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>3</td>
</tr>
<tr>
<td>Oedema</td>
<td>3</td>
</tr>
<tr>
<td>Infection</td>
<td>17</td>
</tr>
<tr>
<td>Skin rash</td>
<td>13</td>
</tr>
<tr>
<td>Headache</td>
<td>3</td>
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</table>

* From reference number 54