

Indications for Imatinib Mesylate Therapy and Clinical Management

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Key Words. Imatinib · Protein tyrosine kinase · Chronic myeloid leukemia, therapy

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Describe the mechanism of action (i.e., the molecular targets) of the anticancer drug imatinib mesylate.
2. Explain how inhibition of these targets confers clinical benefits in specific human cancers.
3. List the most common clinical side effects of imatinib treatment.
4. Manage the side effects of imatinib treatment so as to allow optimal patient management.

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ABSTRACT

Imatinib mesylate (Gleevec®, Glivec®, formerly STI571; Novartis Pharma AG; Basel, Switzerland) is a rationally-designed, molecularly-specific oral anticancer agent that selectively inhibits several protein tyrosine kinases central to the pathogenesis of human cancer. It has demonstrated remarkable clinical efficacy in patients with chronic myeloid leukemia and malignant gastrointestinal stromal tumors. Treatment with imatinib is generally well tolerated, and the risk for severe adverse effects is low. Adverse effects most commonly include mild-to-moderate edema, nausea and vomiting, diarrhea, muscle cramps, and cutaneous reactions. Hepatic transaminase level elevations and myelosuppression occur less frequently and resolve with interruption of imatinib therapy. In general, the incidence and severity of adverse effects tend to correlate with imatinib dose and, in chronic myeloid leukemia patients, the phase of disease; but, patient age and other factors are also associated with some types of reactions. With prompt and appropriate intervention, adverse effects in imatinib-treated patients have proven to be manageable across the spectrum of severity, and they seldom require permanent cessation of therapy. Dose reduction is not usually necessary, and reduction to subtherapeutic levels is not recommended. *The Oncologist* 2004;9:271-281

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INTRODUCTION

Imatinib mesylate (Gleevec®, Glivec®, formerly STI571; Novartis Pharma AG; Basel, Switzerland) is a recently developed oral anticancer agent rationally designed to selectively inhibit certain protein tyrosine

kinases implicated in oncogenesis (Fig. 1). Protein tyrosine kinases control the activation of signal transduction pathways that regulate critical cellular processes, such as growth, differentiation, and apoptosis. They are functionally dysregulated and overexpressed in a number of human

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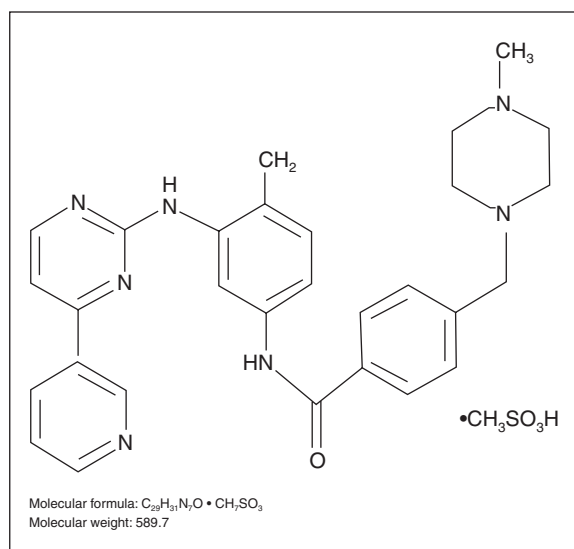


Figure 1. Molecular structure of imatinib mesylate.

cancers [1]. The Philadelphia chromosome (Ph) translocation—t(9;22)—found in chronic myeloid leukemia (CML) results in the generation of a constitutively active fusion tyrosine kinase, Bcr-Abl, which is responsible for the pathogenesis of the disease [1, 2]. Imatinib potently inhibits Bcr-Abl and blocks proliferation and growth of tumor cells expressing *bcr-abl* or *v-abl* [3, 4].

Imatinib is also a potent inhibitor of two cell-surface protein tyrosine kinases, the platelet-derived growth factor receptor (PDGF-R) and the stem-cell factor receptor (c-Kit) [4]. Activation of c-Kit, often in association with a mutation of the *c-kit* proto-oncogene, is believed to be present in all cases of gastrointestinal stromal tumor (GIST) [5]. Dysregulated PDGF-R function is associated with gliomas, myeloproliferative disorders, melanomas, carcinomas, and sarcomas, including dermatofibrosarcoma protuberans [1].

Imatinib has had a dramatic impact on the clinical management of cancers in which this agent has demonstrated efficacy. It is currently approved for the first-line treatment of adult patients with newly diagnosed Ph⁺ CML at all stages and of patients with c-Kit⁺ metastatic or unresectable malignant GIST. In pediatric patients, imatinib is approved in the U.S. for chronic phase patients with recurrence after stem cell transplant or with resistance to interferon therapy; it is approved for all phases of CML in the E.U. Promising results of imatinib treatment have been reported in cases of other diseases, such as hypereosinophilic syndrome (HES) and dermatofibrosarcoma protuberans. In light of the current experience with imatinib, physicians can anticipate a need for long-term clinical management of increasing numbers of patients receiving imatinib therapy. This review addresses the practical aspects of imatinib administration, particularly the

most common types of adverse events, as well as strategies for managing them. Given the emerging importance of sustained imatinib at full therapeutic dosages for optimal cytogenetic and molecular responses [6-9], preventing discontinuation due to adverse events is a crucial management goal.

EFFICACY OVERVIEW

Chronic Myeloid Leukemia

Imatinib demonstrated high levels of efficacy at all stages of CML from the outset of clinical testing in phase I and phase II trials [10-14]. The phase I studies were dose-escalating trials in which the daily doses of imatinib ranged from 25-1,000 mg. A maximum tolerated dose was not identified [10]. In one phase I study [12], which evaluated the 400-mg/d dose of imatinib in patients with chronic-phase disease, 95% of patients achieved complete hematologic response (CHR), and 60% achieved major cytogenetic response (MCR). In two other phase I studies, which evaluated imatinib at doses of 300-1,000 mg/d [10, 11], CHR rates were 98% and 14% for patients in chronic phase and blast crisis, respectively, and MCR rates were 31% and 12%, respectively. In phase II studies in patients with advanced disease [15], CHR rates with imatinib (400 mg/d) were 27% and 0%, and MCR rates were 16% and 6% for patients in the accelerated phase [13] and in blast crisis [14], respectively. Comparable rates with the 600-mg/d dose were: CHR, 37% and 9%; MCR, 28% and 18%.

Based on recently reported findings of the phase III International Randomized IFN versus STI571 (IRIS) trial [16, 17], imatinib is now the gold standard for first-line pharmacotherapy of CML. The IRIS study included 1,106 patients with newly diagnosed CML in chronic phase who were randomly assigned to initial treatment with one of the two study regimens: imatinib (400 mg/d) or interferon (IFN, 5 MU/m²/d) plus cytarabine (Ara-C, 20 mg/m²). After a median follow-up of 19 months, imatinib-treated patients, compared with those receiving the combination, had significantly ($p < 0.001$) higher rates of CHR (95.3% versus 55.5%), MCR (85.2% versus 22.1%), and complete cytogenetic response (CCR) (73.8% versus 8.5%). The estimated rate of freedom from progression at 18 months was also significantly greater in the imatinib (96.7%) than in the IFN (91.5%) group ($p < 0.001$). Superior molecular responses were achieved with imatinib, as demonstrated at the 12-month follow-up, by >3 log reductions in the levels of *bcr-abl* transcripts in 39% of the patients who received this agent, versus 2% of those given IFN plus Ara-C ($p < 0.001$). Reduction in leukemic load has been found, in previous studies, to correlate with duration of remission [7]. Imatinib was also better tolerated than the IFN-based therapy. A

comparison between second-line imatinib administration after IFN failure in the phase II study of patients with chronic-stage CML and first-line treatment in the IRIS trial showed a more favorable side-effect profile associated with first-line use [18].

Gastrointestinal Stromal Tumor

High rates of objective response were achieved in phase I and phase II studies of imatinib therapy for GISTs, a tumor historically resistant to conventional chemotherapy and radiation therapy (Table 1) [19, 20]. Imatinib doses up to 400 mg twice a day were well tolerated in the phase I study, in which 32 of 36 GIST patients achieved inhibition of tumor growth [19]. More than half the patients in the phase II trial had decreases in tumor burden $\geq 50\%$ with no disease progression or development of new lesions. Both the 400-mg and 600-mg daily doses of imatinib were well tolerated [20].

Other Conditions

Therapy with imatinib produced durable responses in a small study of patients with chronic myeloproliferative disorders associated with activation of PDGF-R β [21]. In a patient with unresectable, metastatic dermatofibrosarcoma protuberans (a fibrohistiocytic tumor caused by *COL1A1-PDGFB* fusion), treatment with imatinib (400 mg twice a day) resulted in a 75% reduction in tumor volume, allowing for resection of the mass, which showed complete histologic response [22].

Successful treatment of HES patients with imatinib was reported in several small studies [23-27]. Responses were

achieved in the majority of patients, including rapid normalization of eosinophil count and improvement in other hematologic parameters. In a recently reported study, investigators discovered a fusion of the Fip1-like 1 (*FIP1L1*) and PDGF-R α (*PDGFRA*) genes, resulting in expression of a constitutively activated tyrosine kinase, in 9 of 16 patients with HES; 11 of the 16 patients were treated with imatinib, 9 of the 11 treated patients had CHR lasting more than 3 months, and five of the nine patients with sustained complete responses had the *FIP1L1-PDGFR* gene [28]. These findings demonstrate the presence of a specific target of imatinib in perhaps half or more of the patients with HES. Stem-cell factor activation of c-Kit expressed by eosinophils leads to eosinophil proliferation, and this mechanism has also been hypothesized to play a role in HES [23, 29].

MANAGING COMMON SIDE EFFECTS OF TREATMENT

As with cytotoxic chemotherapies and other interventions for cancer generally, the benefits of imatinib treatment are accompanied by adverse effects that must be managed to facilitate patient adherence to therapy. Overall, imatinib has been well tolerated in clinical studies. Adverse effects have typically been mild to moderate (grade 1 or 2) and usually manageable without dosage reduction or permanent discontinuation of therapy. Those occurring most frequently include gastrointestinal reactions (nausea, vomiting, and diarrhea), edema, muscle cramps, and rash (Table 2) [18, 20, 30]. In patients treated with imatinib for GIST, hematologic abnormalities are uncommon [19]. In the IRIS trial, 136 of the 318 patients who crossed over from IFN plus cytarabine to imatinib did so because of treatment intolerance, com-

Table 1. Efficacy of imatinib in the treatment of GIST: summary of phase I and phase II trial results

	Phase I ^a	Phase II ^b		
	400-1,000 mg/d (n = 36)	Total (n = 147)	400 mg/d (n = 73)	600 mg/d (n = 74)
	n (%)		n (%)	
Objective response	25 (69)	—	—	—
Partial response	19 (53) ^c	79 (54)	36 (49)	43 (58)
Stable disease	7 (19)	41 (28)	23 (32)	18 (24)
Progressive disease	4 (11)	20 (13)	12 (16)	8 (11)
Not evaluable	NR	7 (5)	2 (3)	5 (7)

NR = not reported.
^avan Oosterom et al. [19].
^bDemetri et al. [20].
^cConfirmed partial response. An additional six responses were either unconfirmed partial responses or 20%-29% regressions according to the Response Evaluation Criteria in Solid Tumors [59].

Table 2. Most common adverse experiences in phase II studies of imatinib^a

Event (% of patients)	CML-MBC ^b (n = 260)		CML-AP ^b (n = 235)		CML-CP ^c (n = 532)		GIST ^c (n = 147)	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Nausea	70	4	71	5	60	2	52	1
Fluid retention/edema	71	12	73	6	66	3	74	1
Superficial edemas	67	5	71	4	64	2	—	—
Other fluid retention events	22	8	10	3	7	2	—	—
Periorbital	—	—	—	—	—	—	48	0
Leg	—	—	—	—	—	—	20	0
Face	—	—	—	—	—	—	10	0.7
Other site	—	—	—	—	—	—	10	0
Eyelid	—	—	—	—	—	—	8	0
Muscle cramps	27	0.8	42	0.4	55	1	—	—
Diarrhea	42	4	55	4	43	2	45	2
Vomiting	54	4	56	3	32	1	13	0.7
Hemorrhage	52	19	44	9	22	2	12	5
Central nervous system hemorrhage	7	5	2	0.9	1	1	0	0
Gastrointestinal hemorrhage	8	3	5	3	2	0.4	3 ^d	3 ^d
Tumor hemorrhage	—	—	—	—	—	—	3	3
Musculoskeletal pain	43	9	46	9	35	2	—	—
Skin rash	35	5	44	4	42	3	31 ^e	3 ^e
Headache	27	5	30	2	34	0.2	26	0
Fatigue	29	3	41	4	40	1	35	0
Arthralgia	25	4	31	6	36	1	4	0
Dyspepsia	11	0	21	0	24	0	11	0
Increased lacrimation	—	—	—	—	—	—	10	0
Myalgia	8	0	22	2	25	0.2	40 ^f	0
Weight gain	5	0.8	14	3	30	5	—	—
Pyrexia	41	7	39	8	17	1	—	—
Abdominal pain	31	6	33	3	29	0.6	26	0.7
Flatulence	—	—	—	—	—	—	22	0
Cough	14	0.8	26	0.9	17	0	—	—
Dyspnea	14	4	20	7	9	0.6	—	—
Anorexia	14	2	17	2	6	0	—	—
Constipation	15	2	15	0.9	6	0.2	—	—
Nasopharyngitis	8	0	16	0	18	0.2	—	—
Night sweats	12	0.8	14	1	10	0.2	—	—
Pruritus	8	1	13	0.9	12	0.8	4	0
Epistaxis	13	3	13	0	5	0.2	—	—
Hypokalemia	13	4	8	2	5	0.2	—	—
Petechiae	10	2	5	0.9	1	0	—	—
Pneumonia	12	6	8	6	3	0.8	—	—
Weakness	12	3	9	3	7	0.2	—	—
Upper respiratory tract infection	3	0	9	0.4	15	0	—	—
Dizziness	11	0.4	12	0	13	0.2	—	—
Insomnia	10	0	13	0	13	0.2	—	—
Sore throat	8	0	11	0	11	0	—	—
Ecchymosis	11	0.4	6	0.9	2	0	—	—
Rigors	10	0	11	0.4	8	0	—	—
Asthenia	5	2	11	2	6	0	—	—
Influenza	0.8	0.4	6	0	10	0.2	—	—

Abbreviations: MBC = myeloid blast crisis; AP = accelerated phase; CP = chronic phase; — = data not reported.

^aAdapted from *Hensley and Ford* [18] and *Demetri et al.* [20].

^bAll adverse events regardless of relationship to treatment.

^cAdverse events considered possibly related to treatment.

^dUpper gastrointestinal tract bleeding or perforation.

^eIncludes dermatitis.

^fIncludes musculoskeletal pain.

pared with four imatinib-treated patients who crossed over for this reason [17]. The side-effect profile of imatinib in the IRIS trial was consistent with those seen in previous imatinib studies and substantially better than that of the IFN-Ara-C combination, which was associated with much higher rates of grade 3 and grade 4 toxicities (Table 3).

Gastrointestinal Reactions

Nausea is the most common side effect of treatment with imatinib, occurring in approximately 40%-60% of patients

with chronic-phase CML or GISTs and approximately 70% of patients with advanced CML. It is usually mild (grade 1) and related to dosage [31]. Imatinib is best taken with food, preferably with the largest meal of the day [31]. Ingestion with food does not affect the pharmacokinetic properties of the drug [32]. If the patient has a history of esophagitis or hiatal hernia, imatinib should be taken at least 2 hours before bedtime [30]. Administration of the total daily dosage of imatinib in two divided doses with separate meals may be helpful if patients continue to experience nausea; taking an

Table 3. Adverse experiences occurring in more than 10% of patients in the IRIS trial^a

Event (% of patients)	All grades		Grade 3 or 4	
	Imatinib (n = 551)	IFN + Ara-C (n = 533)	Imatinib (n = 551)	IFN + Ara-C (n = 533)
Superficial edema	55.5	9.2	0.9	0.6
Nausea	43.7	61.4	0.7	5.1
Muscle cramps	38.3	11.1	1.3	0.2
Musculoskeletal pain	36.5	42.0	2.7	8.3
Rash	33.9	25.0	2.0	2.3
Fatigue	34.5	65.5	1.1	24.4
Diarrhea	32.8	41.7	1.8	3.2
Headache	31.2	42.6	0.4	3.2
Joint pain	28.3	39.6	2.4	7.3
Abdominal pain	27.0	24.6	2.4	3.9
Nasopharyngitis	22.0	8.3	0	0.2
Myalgia	21.4	38.8	1.5	8.1
Hemorrhage	20.9	20.6	0.7	1.5
Vomiting	16.9	27.4	1.5	3.4
Dyspepsia	16.2	9.2	0	0.8
Pharyngolaryngeal pain	16.0	13.3	0.2	0.2
Cough	14.5	22.3	0.2	0.6
Dizziness	14.5	23.8	0.9	3.4
Upper respiratory tract infection	14.5	8.3	0.2	0.4
Weight gain	13.4	1.7	0.9	0.2
Pyrexia	13.1	39.2	0.7	2.8
Insomnia	12.2	18.8	0	2.3
Depression	10.2	35.5	0.4	12.8
Constipation	8.5	14.3	0.7	0.2
Anxiety	7.3	11.4	0.2	2.6
Dyspnea	7.3	14.3	1.5	1.5
Pruritus	7.3	11.6	0.2	0.2
Rigors	7.3	33.8	0	0.8
Influenza-like illness	7.1	18.6	0	1.1
Night sweats	7.1	15.6	0.2	0.4
Asthenia	5.6	18.6	0.2	3.9
Anorexia	5.3	31.7	0	2.4
Alopecia	4.4	22.3	0	0.6
Increased sweating	3.6	14.8	0	0.4
Weight loss	3.1	17.1	0.2	1.3
Stomatitis	2.9	12.0	0	0.2
Dry mouth	2.2	10.3	0	0.2
Mucosal inflammation	0.7	10.3	0	3.2

^aAdapted from O'Brien et al. [17]. Adverse events regardless of relationship to therapy. Median follow-up period is 19 months.

800-mg daily dose as 400 mg twice a day is recommended [31]. If nausea recurs despite these measures, antiemetic medications (e.g., prochlorperazine, ondansetron) may be effective in controlling this adverse effect [31].

Some patients experience diarrhea while taking imatinib. Like nausea, this adverse effect is dose related and can be easily controlled with antidiarrheal medications. Because the interstitial cells of Cajal, which have a pacemaker function in the intestine, express high levels of Kit, it is possible that diarrhea in imatinib-treated patients is related to c-Kit inhibition [31].

Edema

Edema develops in more than 50% of patients who receive imatinib and is one of the most common side effects of this agent. Edema is usually superficial and mild to moderate in severity, with excessive central fluid retention (e.g., congestive heart failure, pleural effusion, pericardial effusion, pulmonary edema, ascites, anasarca) having been found to occur in <5% of patients in the phase II CML studies and in approximately 1%-3% of imatinib-treated patients overall [18, 31]. Peripheral edema has been observed most frequently in the legs; about 20% of the patients in the phase II trial of imatinib for GIST experienced grade 1 or grade 2 swelling of the lower extremities. In the phase II studies of imatinib in CML, episodes of grade 3 or grade 4 edema and fluid retention were more prevalent in patients with advanced disease than in those at the chronic stage.

Univariate analysis of adverse event data from the phase II trials of imatinib in CML showed that higher levels of drug exposure (measured by steady-state plasma concentration) were associated with higher risk for edema. However, multivariate analysis demonstrated that this correlated with patient age (>65 years) and sex (female) [18, 31]. A history of cardiac disease or renal insufficiency also appears to be a risk factor for edema and fluid retention [31].

Periorbital edema is the most common type of tissue swelling seen in patients receiving imatinib and tends to be most bothersome in the morning [31]. Imatinib need not be withdrawn in most cases, and no specific therapy is usually required. Reduction of salt intake has helped to relieve symptoms in some patients [31, 33, 34]. In more severe cases, diuretic therapy may be indicated, and a topical 1% hydrocortisone or 0.25% phenylephrine preparation may be beneficial [31, 35]. A single unusually severe case of periorbital edema has been reported in which visual obstruction due to lower eyelid festoons was successfully treated with surgical debulking [33].

As previously noted, severe fluid retention has been observed rarely in patients treated with imatinib. Noncardiogenic pulmonary edema is a generally recognized, albeit

unusual, complication of anticancer therapy [36]. Cerebral edema was reported in two patients, aged 61 and 68 years, who were initially treated with 600 mg/d of imatinib for blast-crisis CML. These are the only two known cases of cerebral edema among 14,000 patients treated worldwide [37]. In a reported case of cardiac tamponade relieved with surgical drainage, edema symptoms resolved 2 weeks postoperatively with diuretic therapy and discontinuation of imatinib [38].

Monitoring of body weight, heart- and lung-associated signs and symptoms, as well as peripheral tissue tone can facilitate early detection of possible fluid retention in patients receiving imatinib [35, 36, 38]. All patients, especially the elderly or those with cardiac or renal impairment, should be monitored particularly closely for edema and fluid retention not responding optimally to diuretics. Initiation of imatinib therapy at a dosage of 300 mg/d with subsequent escalation to 400 or 600 mg/d as tolerated may be considered for patients with risk factors for edema [31]. Evidence of peripheral edema or rapid weight gain warrants prompt initiation of diuretic therapy or an increase in the diuretic dose. If severe fluid retention occurs, imatinib should be discontinued and edema should be controlled with diuretics. Then, an attempt should be made to reinstitute imatinib treatment, possibly through dose escalation, while maintaining diuretic therapy at the required level [31].

Cutaneous Reactions

Approximately 31%-44% of patients experience cutaneous reactions during imatinib administration. The majority of imatinib-related cutaneous reactions consist of generalized rashes that are self-limiting in most cases and can be managed successfully with symptomatic support while imatinib therapy is continued [31]. Patients responding to treatment with imatinib should continue therapy if at all possible for as long as their disease response continues, as such patients usually lack alternatives for treatment of their cancers.

Specific causes of imatinib-related cutaneous reactions have not been identified. Because of its relatively low molecular weight, imatinib is unlikely to be immunogenic [39]. The dose dependency of adverse events supports the hypothesis that imatinib-related cutaneous reactions are mediated by changes in tyrosine kinase signaling rather than immunologic mechanisms [40, 41]. Mast cells and epidermal melanocytes express c-Kit [42]. While stimulation, rather than inhibition, of c-Kit has been proposed as a causative mechanism in atopic dermatitis [42], the possibility that altered c-Kit affects the development of epidermal inflammation and other changes in epidermal homeostasis merits further investigation. There is a report of localized depigmentation in a CML

patient after 6 months of treatment with imatinib, possibly related to inhibition of the melanocyte c-Kit receptor tyrosine kinase [43]; vitiligo has also been reported. Interestingly, progressive repigmentation of the hair during imatinib treatment has also been observed [44]. These pigmentation changes required no intervention.

Among the CML and GIST patients in phase II studies of imatinib, rash and dermatitis were the most commonly reported cutaneous reactions and were typically mild or moderate (grade 1 or 2); serious dermatologic conditions were rare, occurring in approximately 3% of patients. Data from the major phase I and phase II studies suggest that the incidences and severities of cutaneous reactions to imatinib were dose dependent. A small study of cutaneous reactions in imatinib-treated patients confirmed the relationship between dosage on the one hand and rash and edema on the other, with female sex also being an independent risk factor [45].

The most common rash in patients receiving imatinib is characterized by macropapular lesions appearing most prominently on the forearms, trunk, and, occasionally, the face; pruritus is frequent [32]. Severe (grade 3 or 4) exfoliative rashes have been reported in 0.5% of patients treated with imatinib in one study [18]. Across all studies, involving 12,000 patients treated with imatinib for CML, the incidence of severe exfoliative rashes was approximately 1:500, and they generally occurred early in the course of treatment [18].

There are a few reports of single cases of dermatologic reactions in imatinib-treated patients. Three cases of acute generalized exanthematous pustulosis have been reported, as well as two cases of Stevens-Johnson syndrome, both in patients receiving imatinib for treatment of blast-crisis CML [40, 46-48]. One case each of pityriasis rosea and oral lichenoid reaction, possibly related to imatinib treatment, have also been described [49, 50]. The cutaneous reactions in these cases resolved after withdrawal of imatinib and institution of appropriate therapy for the dermatologic condition. Although imatinib was postulated to be the likely cause, confounding factors such as concomitant medications (e.g., allopurinol, sulfamethoxazole/trimethoprim), donor lymphocyte infusion, and possible viral infection were cited in some of the reports. Interestingly, improvement in pre-existing dermatologic disease has also been observed: a 64-year-old male patient with erythrodermic psoriasis of 22 years' duration experienced substantial regression of his psoriatic lesions during treatment with imatinib for metastatic GIST [51].

For drug-related cutaneous eruptions in general, early recognition of symptoms, withdrawal of the causative agent, and prompt initiation of symptomatic treatment are the mainstays of therapy [52, 53]. Vigilance is particularly warranted in the initial weeks of imatinib treatment. However,

if equally effective alternative drugs are not available, it may be necessary to continue a course of treatment despite the presence of a cutaneous reaction [39].

Symptomatic management with antihistamines, salves, and coal tar preparations has proven useful in patients with mild-to-moderate imatinib-associated rashes. Topical or short-course oral glucocorticoid treatment can be used in patients unresponsive to more conservative measures [31]. Antihistamine prophylaxis may be considered for the rare patient with an extremely elevated basophil count (>20%) [31].

Gradual dose escalation has made it possible to reinstitute imatinib therapy after the resolution of even severe desquamative rashes [31, 54]. The use of prednisone (1 mg/kg/d, tapered to 20 mg/d over several weeks) and gradual reintroduction of imatinib (100 mg/d initially, increased by 100 mg per week as the prednisone dose is being tapered provided the rash does not recur) has been an effective strategy for achieving long-term tolerance of therapeutic doses of imatinib after a severe skin reaction in patients without alternative antineoplastic treatments [31]. Adverse skin effects in imatinib-treated patients have been successfully managed across the spectrum of severity.

Muscle Cramps/Myalgia

Musculoskeletal complaints—pain, muscle cramps, myalgia, arthralgia—are commonly associated with imatinib therapy, affecting about one-quarter to one-half of patients. As with other frequently occurring side effects, muscle pain is usually mild to moderate and manageable without reduction of the imatinib dose.

Muscle cramps in imatinib-treated patients usually occur in the hands, feet, calves, and thighs, and some patients may describe them in terms reminiscent of tetanic contractions. The cramps tend not to change over time with respect to pattern, frequency, and severity. They do tend to have consistent triggers, and patients report experiencing them mainly at night or with exertion. The cause of this side effect is unknown [31].

Although patients undergoing imatinib therapy have not been found to have abnormal levels of ionized calcium and magnesium, the use of calcium supplements has provided relief from muscle cramps, and it is possible that magnesium supplements may occasionally be of some help as well. Some patients' symptoms have responded to quinine supplementation [31].

Liver Transaminase Elevations

Data from preclinical and clinical studies of imatinib indicate that vigilance for possible hepatotoxicity should be part of the approach to managing imatinib therapy. Mild transaminitis is the most common manifestation in imatinib-treated patients, although elevated bilirubin levels

have also been observed [30]. In the phase II CML studies, approximately 2%-3% of patients had grade 3 elevations in their levels of aspartate aminotransferase (AST), with no grade 4 elevations; grade 3 elevations in alanine aminotransferase (ALT) occurred in about 2%-4% of patients and grade 4 elevations were seen only in blast-crisis patients (0.4%) [18]. The incidence of grade 3 or 4 abnormalities in liver function test results was similar for GIST patients—approximately 3% [20]. In the IRIS trial, among patients with newly diagnosed chronic-phase CML, 5.1% of the imatinib-treated patients and 6.8% of the patients given the IFN-based regimen had elevated AST or ALT levels of grade 3 or 4 [17]. The precise cause of abnormal transaminase levels in patients receiving imatinib is not known, although liver biopsy findings are consistent with those of a typical drug-induced hypersensitivity response [31]. Imatinib is principally metabolized by hepatic cytochrome P-450 isoenzymes.

Elevated transaminase levels in affected patients generally appear during the first 2-3 months of imatinib therapy and typically resolve in approximately 14-21 days upon drug withdrawal [18, 35]. Imatinib can be reinstated in most instances (Table 4). Late-onset liver toxicity has been reported in a few patients, at approximately 293-541 days after the start of treatment [18]. These late events resolved over a median period of 73 days after discontinuation of imatinib, and therapy was able to be resumed without recurrence of transaminase elevation in a subset of cases. In a case report of two patients with GIST

and impaired liver function, imatinib was administered under close surveillance without unusual side effects during a follow-up period of 3-4 months [55].

Liver function testing is recommended before the start of imatinib therapy, every other week during the first month of treatment, and at least once a month thereafter [31]. Patients with elevated transaminase levels should be monitored more frequently. Evaluation for a possible infectious cause may also be considered [56]. Table 4 summarizes suggested management approaches [30].

Considerations for Patients with Renal Impairment

Imatinib and its metabolites are not significantly excreted by the kidneys and, until recently, no specific studies had been conducted in patients with impaired renal function. However, a phase I pharmacokinetic study of imatinib in patients with varying degrees of renal dysfunction and a variety of tumor types (including GIST) was reported at the 2003 meeting of the American Society of Clinical Oncology [57]. In the study, plasma clearance decreased with worsening renal dysfunction; however, the toxicity profile of imatinib did not appear to be adversely affected by mild-to-moderate renal dysfunction. Nevertheless, a single episode of dose-limiting toxicity was observed in one patient with moderate renal dysfunction taking 200 mg of imatinib, therefore, caution should be observed when administering imatinib to patients with impaired renal function because of their lower capacity to metabolize the drug.

Table 4. Considerations for liver function monitoring during imatinib therapy^a

General

- Obtain LFT results before initiation of imatinib
- Obtain LFT results every other week during first month of treatment
- Obtain LFT results at least monthly after the first month of treatment
- Test more frequently if patient has elevated transaminase levels

Grade 2 ALT/AST elevation (2.5-5 times the ULN)

- Review intake of potential hepatotoxins (e.g., acetaminophen, ethanol); substitute for nonessential hepatotoxic medications if possible
- Persistent elevation:
 - Consider more extensive evaluation (e.g., viral hepatitis panel, ferritin level, alpha-1-antitrypsin level, ultrasonography, liver biopsy)
 - Assess continuation of imatinib therapy in light of clinical situation; dose reduction may be warranted

Grade 3 ALT/AST elevation (>5 times the ULN)

- Interrupt imatinib therapy and monitor LFTs
- Reintroduce imatinib at reduced dose when LFT results fall to grade 1 levels or lower (ALT/AST <2.5 times the ULN; bilirubin <1.5 times the ULN)
- If no recurrence within 6-12 weeks: consider re-escalation to initial dose, with close LFT monitoring
- If recurrence: perform more extensive evaluation, as described above; discontinue imatinib therapy^b

Abbreviations: LFT = liver function test; ULN = upper limit of normal.

^aData from *Deininger et al.* [31].

^bPermanent discontinuation of imatinib therapy owing to persistently elevated LFT values has been required in <1% of patients.

Myelosuppression

The development of myelosuppression is significantly more common in CML than in GIST patients receiving imatinib [19]. In the phase II trial of imatinib in patients with late chronic-stage CML, 27% had grade 3 and 8% had grade 4 neutropenia, 19% had grade 3 and <1% had grade 4 thrombocytopenia, and 6% had grade 3 and 1% had grade 4 anemia [12]. In the IRIS trial with early chronic-stage patients, the incidences of grade 3 or grade 4 neutropenia, thrombocytopenia, and anemia were less than half those seen late in the chronic phase (Table 5) [17]. The higher incidence of myelosuppression in patients with longer duration of chronic-phase CML mirrors the pattern found in the studies involving accelerated-phase and blast-crisis patients: myelosuppression generally became more prevalent and more severe at progressively later stages of the disease [13, 14, 18]. In imatinib-treated GIST patients, myelosuppression is infrequent and is not dose dependent. Mild anemia and mild-to-moderate neutropenia have been most commonly reported [19, 20]. In the phase II study of imatinib in GIST patients, 9% of the patients had anemia (2% grade 3 or grade 4), 7% had neutropenia (5% grade 3 or grade 4), and 5% had leukopenia (1% grade 3 or grade 4) [20].

In addition to advanced disease, factors associated with a greater risk for myelosuppression in CML patients treated with imatinib include a low hemoglobin level, history of IFN-induced cytopenias, and prior busulfan therapy [31]. Because most hematopoiesis in patients with CML stems from the Bcr-Abl clone, myelosuppression is to be anticipated as a therapeutic effect. Imatinib minimally inhibits normal hematopoiesis [31] and, therefore, should rarely, if ever, be given at dosages below the therapeutic threshold of 300 mg/d. It is best to use at least the approved dosages whenever possible: 400 mg/d for CML in chronic phase and 600 mg/d for CML in accelerated phase and blast crisis, with judicious escalation to 800 mg/d (400 mg twice a

day) if there is relapse or lack of response [35]. Recently, myelosuppression has been identified as an independent adverse risk factor for achieving a cytogenetic response with imatinib in patients with CML [58]. Treatment with hematopoietic growth factors may provide some benefit, but combination therapy with imatinib and growth factors has yet to be evaluated in trials.

Because myelosuppression can be severe and prolonged in some patients treated with imatinib, it is important when administering this agent to exercise appropriate caution, especially with patients whose residual normal hematopoiesis is limited, and to manage treatment intensity in light of the phase of disease [31]. In patients with chronic-phase CML, the following steps have been recommended [31]:

- Withhold imatinib if the absolute neutrophil count (ANC) declines below 1,000/mm³ or the platelet count is less than 50,000/mm³
- Resume imatinib therapy when the ANC recovers to >1,500/mm³ and platelets exceed 100,000/mm³ (Take into consideration any factors, such as increased percentage of blasts or basophils and clonal evolution, that confer higher risk. More severe disease may justify continuation of treatment in the presence of lower blood cell counts, particularly if they reflect disease effects.)
- If recovery occurs in less than 4 weeks, reinstitute imatinib at 400 mg/d
- If more than 4 weeks are required for recovery of peripheral counts, consider a dosage reduction to 300 mg/d; the dosage can be raised to 400 mg/d as long as myelosuppression does not recur for at least 4 weeks

As previously noted, it is inadvisable to give subtherapeutic dosages of imatinib (i.e., less than 300 mg/d). Dose interruption for recurrent myelosuppression is the preferred strategy [31].

SUMMARY

Imatinib is a novel, molecularly targeted anticancer drug that demonstrates remarkable clinical activity in patients with CML, GIST, and other tumors caused by imatinib-specific abnormalities of PDGF-R and c-Kit. The most common side effects associated with imatinib treatment, which are generally mild to moderate, include edema, nausea and vomiting, diarrhea, muscle cramps, and cutaneous reactions. Myelosuppression and elevated liver transaminase levels also occur, warranting maintenance of appropriate monitoring and, if necessary, consideration of a

Table 5. Incidence of grade 3 or grade 4 hematologic and biochemical abnormalities in the IRIS trial^a

Event	Imatinib	IFN + Ara-C
	(n = 551)	(n = 533)
	% of patients	
Anemia	3.1	4.3
Neutropenia	14.3	25.0
Thrombocytopenia	7.8	16.5
Elevated serum ALT or AST level	5.1	6.8

^aData from O'Brien et al. [17].

dosage adjustment within the therapeutic range or a strategy of drug withdrawal and rechallenge.

Experience to date has demonstrated that the earliest possible initiation of treatment with imatinib and the use of full therapeutic dosages are crucial to achieving optimal clinical responses. Like most cancer therapies, imatinib is associated with a range of side effects. In the case of imatinib, these have proven to be manageable across

the spectrum of severity and seldom present a permanent barrier to continued therapy. Prompt and aggressive intervention to control side effects is an important facet of successful imatinib administration. Such intervention can enable imatinib treatment to continue in most patients with CML or GIST at therapeutic doses or to be reinstated after the resolution of an adverse event, when appropriate.

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