Improving diagnosis and treatment of gastrointestinal stromal tumor (GIST) patients: Results from the Dutch GIST Registry

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Chapter 3

Adverse events

Paragraph 3.1

Imatinib-induced agranulocytosis in patients with gastrointestinal stromal tumors

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Abstract

Agranulocytosis is a rare but serious side effect of imatinib in gastrointestinal stromal tumor (GIST) patients. Imatinib is an inhibitor of the proto-oncogene tyrosine kinase (c-KIT) and the first-line agent in patients with locally advanced and metastatic GIST. Little evidence is available on the management of this adverse event, and consensus-based guidelines are lacking. In this article, we describe 4 patients with agranulocytosis after starting imatinib. In addition, an overview of the available literature concerning the underlying mechanisms is given, and therapeutic strategies for overcoming this adverse event are discussed. In our experience it appears safe to restart imatinib after normalization of neutrophil count. In case of relapse of agranulocytosis, reintroduction combined with prednisolone, with treatment with granulocyte colony-stimulating factor or dose reduction can be considered

Introduction

Gastrointestinal stromal tumors (GISTs) are rare mesenchymal tumors originating from the gastrointestinal tract. Constitutive activation of KIT receptor tyrosine kinase plays a pivotal role in the pathogenesis of GIST. Imatinib (Glivec, Gleevec) is a selective tyrosine kinase inhibitor active against the proto-oncogene c-KIT (CD117), BCR-ABL (or Philadelphia chromosome in chronic myeloid leukemia) and platelet-derived growth factor receptor (PDGFR) tyrosine kinases. Currently, imatinib is the standard treatment in locally advanced and metastatic GIST patients. Furthermore, imatinib has been approved for patients with chronic myeloid leukemia (CML).

Overall, imatinib therapy is well tolerated. Common side effects are periorbital edema, nausea, diarrhea, muscle cramps, fatigue, and skin rash. Dose-dependent hematologic toxicity affecting all hematopoietic lineages to a variable degree is observed clinically, especially in imatinib-treated CML patients.(1) In GIST patients treated with imatinib grades 3–4, neutropenia is reported in 4.8% of all cases.(2) Nevertheless, imatinib-induced complete agranulocytosis (a neutrophil count less than 0.1 103/ mL) is thought to be a rare adverse event.(3) After a first episode of imatinib-induced agranulocytosis treating clinicians are often reluctant to restart this effective drug.

In this article we report 4 GIST patients with imatinib-induced agranulocytosis (Table 1). In addition, we give an overview of available literature regarding the possible underlying mechanisms and the different therapeutic strategies for overcoming this adverse event. Finally, we give our recommendations for treating imatinib-induced agranulocytosis.

Case Reports

Patient A, an 87-year-old man, presented with a large intra-abdominal tumor (7.0 6.5 cm) and pulmonary lesions. Biopsy of the abdominal mass showed a GIST (mitotic index, 4/10 HPF; *KIT* exon 11 mutated). His medical history included restless legs syndrome, gastro-esophageal reflux disease, and locally advanced prostate cancer (T3bN0M0) 1 year earlier, for which he was treated with radiotherapy and hormonal therapy. His medications included goserelin implant, tolterodine, tamsulosine, hydroquinine, pantoprazole, and acetaminophen. Baseline laboratory testing showed a decreased hemoglobin level (Hb, 10.3 g/dL; range, 14.0–17.5 g/dL); all other bone marrow and organ functions were normal. Treatment with imatinib at a dose of 400 mg daily was commenced. Five weeks later he was admitted to our hospital because of fever and hypotension (90/50 mmHg). Further physical examination was unremarkable. Laboratory testing showed an Hb of 9.2 g/dL, white blood cell count (WBC) of 8.3 x 10^3/mL (range: 4.0–10.5 x 10^3/mL) with a complete agranulocytosis (absolute neutrophil count (ANC) < 0.1 x10^3/mL; range: 1.8–7.2 x 10^3 /mL) and thrombocytopenia (119 x 10^3 /mL; range: 150–400 x 10^3 /mL). Imatinib was discontinued, and broad-spectrum antibiotics were initiated. As a possible contributing

factor to neutropenia, hydroquinine was stopped. Further investigation including urine analysis and culture, chest x-ray, and blood cultures did not reveal a source of infection. He was afebrile on the second day, and he was discharged from the hospital on the sixth day. Full neutrophil recovery was reached 10 days after imatinib discontinuation. Three weeks after discharge, imatinib was restarted (400 mg/day) with weekly monitoring of blood levels. Six weeks afterward, the ANC dropped to 0.5 x 10^3/mL. Imatinib was discontinued again, and now ANC normalized within 2 weeks (2.2 x 10^3/mL). Within 1 month, 400 mg imatinib once daily was restarted in combination with 10 mg prednisolone. After 3 months of prednisolone, the dose was decreased to 10 mg every other day and stopped a week later. Eight months later, agranulocytosis did not recur, and the patient remained progression-free.

Patient B, a 41-year-old woman, underwent incomplete surgical resection of a multinodular gastric GIST (7 cm, spindle cell type, c-KIT positive, mitotic index 0/50 HPF). At the time of diagnosis, metastases in the liver and intra-abdominal lymph nodes were present. Palliative imatinib treatment at a dose of 400 mg daily was commenced. Baseline laboratory testing revealed mild normocytic anemia (Hb: 11 g/dL; MCV: 81 mm^3), WBC 8.9 x 10^3/mL, and ANC 7.1 x 10^3/mL. One month after initiation of systemic treatment, she was admitted because of fever. Laboratory testing showed a microcytic anemia (Hb: 10.3 g/dL; MCV: 78 mm^3), WBC 1.9 x 10^3/mL, and ANC 0.17 x 10^3/mL. Two days later the ANC dropped below the detection threshold (0.05 x 10^3/mL). Imatinib was discontinued, and broad-spectrum antibiotics were started. Because of ongoing neutropenia on the fifth inpatient day, bone marrow examination was performed revealing impaired granulopoiesis. A maturation arrest of neutrophils in the myelocyte stadium was seen without any other abnormalities. In addition, "normal" bowel tissue and neutrophil granulocytes in blood were screened for *KIT* exon 11 mutations. No mutations could be demonstrated in these samples.

Granulocyte colony-stimulating factor (G-CSF; 300 mg daily) was given for 5 days, resulting in rapid normalization of the ANC (18.5 x 10^3/mL). Further investigation did not reveal a source of infection, and she was discharged with a good clinical condition. Repeated bone marrow examination 2 weeks after discharge was unremarkable. Imatinib was restarted at a dose of 300 mg daily. Two weeks later neutropenia recurred (ANC: 1.2 x 10^3/mL), and imatinib was discontinued. Full neutrophil recovery was reached 1 week later, and imatinib was restarted (300 mg). Routine laboratory tests in the following 3 months were normal. Then imatinib was stopped because of imatinib-induced hepatitis. No alternative treatment was started. Follow-up computed tomography (CT) scans showed no progression of the residual lesions in the last 11 years.

Patient C, a 45-year-old woman, was diagnosed with an abdominal tumor (8.1 x 7.9 cm) originating from the small bowel. Ultrasound-guided biopsy showed a wild-type GIST. Neoadjuvant treatment with imatinib (400 mg daily) was started. The patient was taking no other medication. Baseline laboratory testing was unremarkable. One month after

starting imatinib, she complained of fever, chills, and a sore throat. Laboratory testing showed a WBC of 3.1 x 10^3/mL and an ANC of <0.1 x 10^3/mL. Imatinib was promptly discontinued, and she was admitted for the administration of broad-spectrum antibiotics and G-CSF (filgrastim 1 x 300 mg). Within 2 days she clinically improved, the fever resolved, and the ANC rose to 0.6 x 10^3/mL. Response evaluation after 1 month showed progressive disease, and an R0 resection of the tumor was performed. Adjuvant imatinib treatment was not given.

Patient D, a 53-year-old man, was found to have a rectal mass during evaluation for rectal bleeding. Biopsy revealed a c-KIT-positive spindle cell wild-type GIST. Laboratory testing showed an Hb of 7.1 g/dL. Neo-adjuvant treatment with imatinib (400 mg daily) was started because of the close relationship of the tumor with the anal sphincter. During routine laboratory testing 1 month after the start of imatinib, an ANC of 0.1 x 10^3/ mL was detected, and imatinib was discontinued. Ten days later the ANC recovered to 3.7 x 10^3/mL, and imatinib was restarted at a dose of once-daily 300 mg. Neoadjuvant treatment with imatinib could be continued for 6 months in total without recurrence of agranulocytosis, CT scans after 3 and 6 months showed a partial response and stable disease, respectively, after which it was planned for the patient to have a resection.

Table 1: Summary of cases described in this article.

Patient	Imatinib Daily Dose	Time to Agranulocytosis	Intervention	Time to Recovery Agranulocytosis	Reintroduction of IM[a]	Recurrence[b]	Cancer-Related Outcome
A							
First episode	400 mg	5 weeks	Stopped until recovery	10 days	Yes	Yes	Progression-free after 8 months
Second episode	400 mg	6 weeks	Reintroduction with prednisolone	2 weeks	Yes	No	
B							
First episode	400 mg	1 month	G-CSF dose and reduction (300 mg)	10 days	Yes	Yes	IM stopped after 3 months due to hepatic toxicity. Progression-free after 11 years
Second episode	300 mg	2 weeks	Stopped until recovery	1 week	Yes	No	
C							
	400 mg	1 month	G-CSF	2 days	No	N/A	Early resection due to progression
D							
	400 mg	1 month	Dose reduction (300 mg)	10 days	Yes	No	Resection after 6 months of therapy

Discussion

Non-chemotherapy drug-induced agranulocytosis is a rare but potentially serious adverse event that is characterized by a decrease in the peripheral neutrophil count to less than 0.5 x 10^3/mL because of cytotoxic or immunogenic mechanisms. The most feared complication of severe neutropenia is the development of potentially lifethreatening infection. In 1 GIST patient, pulmonary tuberculosis secondary to grade 3 imatinib-induced neutropenia was described in 2005 by Takashima et al.(4) Imatinib is a selective tyrosine kinase inhibitor active against c-KIT (CD117), BCR-ABL, and PDGFR tyrosine kinases. Imatinib is approved for treatment of CML and GIST. Myelosuppression can occur at any time during imatinib therapy, but it usually begins within the first 2 to 4 weeks of treatment.(5) In our cases, neutropenia occurred within approximately 1 month after initiation of imatinib. The incidence of hematotoxicity in CML patients treated in the first months was previously described to be most predominant at the start of treatment and to decrease after 18 months.(6) Hematologic side effects are mainly dose-dependent, include all 3 lineages, and are reversible on cessation of treatment. However, 1 study comparing imatinib 400 mg daily with 800 mg daily found no difference in the incidence of neutropenia.(7) Whether the development of imatinib-induced agranulocytosis is related to drug exposure (imatinib drug levels) is unknown. In none of our 4 cases were imatinib drug levels measured. In the future, cases measuring imatinib drug level may provide further insight into the underlying mechanisms of imatinib-induced agranulocytosis.

For now it remains unclear which patients are at risk for developing hematologic toxicity. A low ANC and low hemoglobin concentration at the initiation of imatinib are potential risk factors.(8) The development of myelosuppression is particularly common in CML patients treated with imatinib. In these specific groups, grade 3–4 neutropenia (ANC 0.5–1.0 and <0.5 x 10^3/mL, respectively) was reported to occur in 35%–45% of patients who were treated with 400 mg daily.(9) In CML patients myelosuppression is expected because of suppression of the malignant clone by inhibiting the BCR-ABL.

Interestingly, myelosuppression is also seen in imatinib-treated GIST patients who are assumed to have an uncompromised bone marrow function. That imatinib can affect the function of normal, nonmalignant cells suggests that additional pathways are involved leading to myelosuppression.(6) The c-KIT proto-oncogene (CD117), which is targeted by imatinib, has been shown to be present in several cell types including normal hematopoietic stem cells.(10) However, in vitro studies showed that the inhibitory effect of imatinib on normal CD34þ progenitor cells is largely independent of c-KIT signaling. This suggests that other mechanisms might be involved in the inhibitory effect.(11) The exact mechanism by which imatinib induces its antiproliferative effect on normal CD34+ cells has yet to be clarified. In addition to BCR-ABL and c-KIT, imatinib also inhibits platelet-derived growth factor (PDGF) activity. PDGF has been demonstrated to be an effective cytokine for the ex vivo expansion of normal early stem and progenitor cells.(12) Inhibition of PDGF activity by imatinib can therefore also contribute to myelosuppression.

Significant myelosuppression results in treatment interruptions or dose reduction, which may compromise responses to imatinib. In the case of clear agranulocytosis, cessation of imatinib treatment remains crucial to avoid further hazardous exposure. In patient B, repeated bone marrow examination demonstrated impaired granulopoiesis with a maturation arrest of neutrophils in the myelocyte stadium, which was reversible on cessation of imatinib treatment. All our patients experienced full recovery of the neutrophil count only a few days after discontinuation of imatinib. This is in line with 1 case study on imatinib-induced agranulocytosis in a GIST patient describing agranulocytosis and severe skin rash, which both spontaneously recovered after cessation of therapy.(13)

Limited data are available about the risk of recurrent neutropenia when imatinib is readministered when ANC > 1.5 x 10^3/mL. Rechallenge with imatinib in a slightly reduced dose after agranulocytosis in patient D was uneventful, with normal ANC. Patients A and B experienced recurrence of the neutropenia after imatinib rechallenge. Patient A was able to continue imatinib treatment in combination with prednisolone therapy. Patient B could restart imatinib after the second episode without further hematologic toxicity. Administration of G-CSF in patients B and C might have accelerated neutrophil regeneration.(14) In patients with CML, G-CSF has been shown to be effective in overcoming imatinib-induced neutropenia.(4,15–17) In this way, recovery of neutrophil counts can even be achieved during uninterrupted imatinib therapy. Treatment with G-CSF in nonchemotherapy drug-induced agranulocytosis is associated with a lower median duration of neutropenia (8 days in treated patients vs 9 days in untreated patients, P = 0.015). In this report no significant association between decreased case-fatality rates and use of hematopoietic cell growth factors could be observed.(3) However, imatinib therapy was not included in this analysis, and to our best knowledge, G-CSF administration in imatinib-induced neutropenia in GIST patients has never been studied. It therefore remains questionable whether the use of expensive G-CSF results in a clinical significant benefit and is justified in the absence of severe infection.

Patient A was able to continue imatinib treatment in combination with prednisolone therapy. This strategy was not previously described in imatinib induced agranulocytosis. Considering the short period this treatment is given to the patient and its low cost, this option can be considered. However, one can argue that reintroduction without prednisolone might have been uneventful as well. Furthermore, no immunological response was seen in the patient's bone marrow. Therefore, any possible effect of corticosteroids is unclear. Patient B could restart imatinib after the second episode without further hematologic toxicity. In this case, imatinib was reintroduced in a decreased dose of 300 mg. This strategy was also used in a study describing 13 CML patients receiving G-CSF without discontinuation of imatinib.5 Hwang et al described a dose reduction to 100 mg in 1 GIST patient, without relapse of agranulocytosis or skin toxicity observed.(13) Despite dose reductions all patients in both reports showed response. In Table 2 a summary of

available studies on different treatment strategies for imatinib-induced agranulocytosis is given.

Based on the sparse literature and our, albeit limited, experience in these 4 cases, we propose recommendations for patients with GIST presenting with imatinib-induced agranulocytosis (Figure 1). At the first episode of agranulocytosis, we recommend cessation of imatinib treatment until full neutrophil recovery. When neutrophils are recovered, imatinib can be restarted at the same dose. If there is a relapse of imatinib-induced agranulocytosis, we recommend a rechallenge with dose reduction, or the use of either G-CSF or low-dose corticosteroids in combination with full-dose imatinib. In case of a second relapse or in case of life-threatening relapse, one can consider alternative therapy. This can consist of second-line tyrosine kinase, like sunitinib, or early planned surgery in case of neoadjuvant therapy.

Conclusion

Imatinib-induced agranulocytosis is a rare but potentially serious adverse event with life-threatening infection as the most feared complication. Imatinib is usually effective in locally advanced and metastatic GIST, and a rechallenge with imatinib should be considered after a first episode of agranulocytosis and full recovery of the neutrophil count. In our limited experience this appears a safe approach, with strict monitoring of the hemogram. The use of G-CSF or corticosteroids can be considered. Imatinib treatment should not routinely be withheld to GIST patients encountering a first episode of imatinib-induced agranulocytosis.

Table 2: Summary of available studies on different treatment strategies for imatinib-induced agranulocytosis.

Article	No. of Patients	Primary Disease	Imatinib Daily Dose	Time to Agranulocytosis	Intervention	Time to Recovery Agranulocytosis	Reintroduction of Iimatinib	Outcome
Heim 2003[16]	6	CML	400–600 mg	12–41 days (median, 28days)	G-CSF with continuation of imatinib	1–7 days (median, 6 days) with G-CSF 28–42 days (median, 28 days) before G-CSF	Yes, all patients	1 death (blast crisis)
Heim 2003[16]	3	CML	600 mg	Unknown	Stop imatinib until recovery	Not reported	Yes, 1 patient	2 blast crises 1 CHR but no CCR
Quintas 2004[15]	13	CML	400–800 mg	4–174 days (median 67 days)	G-CSF with continuation of imatinib and dose reduction to 300 mg	Within 21 days (43–144 days) with G-CSF 4–49 Days (median, 20 days) before G-CSF	Yes, all	All alive, all response to imatinib
Takashima 2005[4]	1	GIST	400 mg	5 months	Stop imatinib	Not reported	No	Died 1 year later due to progressive disease
Zaucha 2006[18]	1	CML	600 mg	1 month	G-CSF with continuation of imatinib	No recovery	No	Died of septic shock
Khouri 2008[5]	1	CML	400 mg	1 month	Stop imatinib, start G-CSF	Not reported	Not reported	Alive
Hwang 2009[17]	1	CML	400 mg	3 months	G-CSF 300 mg/day, twice weekly	1 week	Yes	Relapse agranulocytosis, bone marrow examination showed M. Kahler
Hwang 2010[13]	1	GIST	400 mg	3 months	Stop imatinib and wait for recovery	1 month	Yes, with reduced dose of 100 mg due to skin rash	Alive and partial response
Zhao 2011[19]	38	CML	400 mg	12 days in control group 10 days in Berbamine group	Berbamine in combi-nation with imatinib with-drawal	79 (29–132) days in control group 42 (28–88) days in Berbamine group (recovery to ANC >2.0 10^9/L)	Yes	Control: Recurrence of agranulocytosis in 10 of 19 patients CCR in 17 of 29 Berbamine: Recurrence of agranulocytosis in 3 of 16 patients CCR in 23 of 34

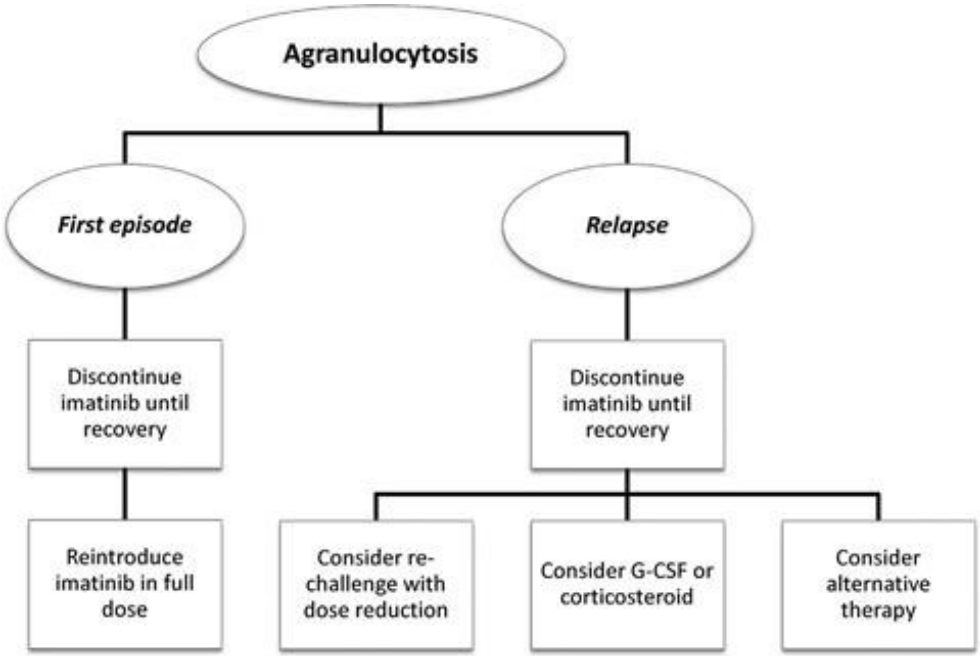

Figure 1: Recommendations for management of imatinib-induced agranulocytosis. When a patient presents with imatinib-induced agranulocytosis, we recommend stopping imatinib and waiting for full recovery. If the patient has a fever, broad-spectrum antibiotics should be administered. After full recovery, imatinib can be reintroduced at the same dose. In case of relapse of agranulocytosis, one should consider a rechallenge with imatinib in combination with dose reduction, granulocyte colony-stimulating factor (G-CSF), or low-dose corticosteroids, that is, prednisone 10 mg once daily. Prednisone dose can be slowly tapered with strict monitoring of the hemogram. One can also move to alternative therapy, for example, second-line therapy or surgery in the case of neoadjuvant therapy.

Declaration of Conflicting Interests

The first and second author equally contributed to the article. All authors listed sufficiently contributed to the article to be included as authors. There is no conflict of interest, financial or other.

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