

Drug- Induced Pneumonitis: A Rare Complication of Imatinib Mesylate Therapy in Patients with Chronic Myeloid Leukemia

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1. Introduction

Therapy by drugs that block the activity of the protein Bcr-Abl, specific inhibitors of Bcr-Abl tyrosine kinase (TKI), significantly changed the prognosis of chronic myeloid leukemia (CML). Bcr-Abl gene is located on the Philadelphia chromosome (Ph'-chromosome), resulting from t(9;22) translocation, plays a key role in the onset and progression of CML. To date, the standard in the treatment of CML patients is imatinib mesylate (Gleevec, "Novartis Pharma AG", Switzerland). In addition, TKI 2nd generation, nilotinib and dasatinib, which differ in activity and impact points, also show encouraging results as first-line therapy of CML. According to an international multicenter study of IRIS (after 60 months of imatinib therapy) is shown that a complete hematologic remission was achieved in 96% of patients, major cytogenetic response - at 92%, complete cytogenetic response - 86% [1]. Imatinib treatment is well tolerated; treatment withdrawal because of intolerance is noted only in 5% of patients [2, 3]. The most frequent side effects are edema (peripheral edema, pleural or pericardial effusion, ascites, and pulmonary edema), rapid increase of body weight (independently from peripheral edema), nausea, vomiting, myalgia, muscle cramps, diarrhea, skin rash [4, 5].

Respiratory side effects of imatinib are rare. The most frequent among them are cough (9–22%), dyspnea (5–16%), flu-like syndrome (11,1%), upper respiratory tract infections (16,5%), pneumonia (1–10%) [4, 5]. Quite infrequent complications are pulmonary fibrosis and drug-induced pneumonitis [6].

We have some cases of such complications in available literature [7, 8, 9, 10, 11, 12]. Signs and symptoms of pneumonitis are similar: constitutional symptoms, malaise, low-grade fever, dyspnea (both exertional and at rest), cough, interstitial pulmonary infiltrates [13]. These symptoms are nonspecific and are often seen in other disorders. Rosado M.F. et al. have published one of the first case reports of imatinib-induced pneumonitis in 63 year-old woman with CML. At month 2 of imatinib treatment she has experienced dry cough and moderate exertional dyspnea. At 5th month of imatinib treatment both cough and dyspnea have worsened and hypoxemia was found (SaO₂ 88%). The diagnosis was confirmed by results of CT scan and bronchoscopy with transbronchial needle aspiration, excluding bacterial, viral and fungal etiology of pneumonitis [8]. J.Rajda et al. have described drug-induced pneumonitis in 77 year-old woman with CML during first 4 weeks of imatinib

treatment. The progressive exertional dyspnea has led to nearly complete disability, where she could feel comfortable only at rest; later on a low-grade fever occurred. SaO₂ was 85% [13]. In other patients the disease manifestations, diagnostic approach and treatment were quite similar.

Although most cases of imatinib-induced pulmonary adverse events have been reported in patients with early chronic phase CML (from 0.2 to 1.3%). Dyspnea during imatinib therapy is most often related to fluid retention and pulmonary edema. Fluid retention may be due to prolonged platelet-derived growth factor inhibition by imatinib. Platelet-derived growth factor pathways are involved in the regulation of interstitial fluid homeostasis [16]. Imatinib pneumonitis develops in the period from 10 to 282 days (median time, 49 days) after treatment with imatinib (range, 200 to 600 mg daily). Dyspnea, hypoxemia and fever are usually seen. The chest CT scan shows diffuse or patchy ground-glass opacity, consolidation, or fine nodular opacity. The lung pathology may show interstitial pneumonitis and fibrosis, destruction of alveolar septa, lymphocytic alveolitis, plasma cell infiltrates, or type II pneumocyte hyperplasia. The resolution of pneumonitis after corticosteroid therapy has been reported. Ohnishi et al [16] reported that pneumonitis developed in 4 of 11 patients with a history of imatinib-induced pneumonitis after reexposure to imatinib [7, 13]. Diagnose lung disease caused by taking drugs is not always easy due to lack of specific clinical and morphological manifestations.

2. Clinical observations

In 2007–2008 in Hematology Research Center (Moscow, Russia) we have observed (including retrospective) in CML patients 4 cases of suspected imatinib-induced pneumonitis (Table 1). Three female and 1 male patients aged 13, 64, 66, and 40 correspondingly have initial diagnosis of chronic phase CML high-risk group, according to Sokal. The CML duration before imatinib treatment was 24, 11, 2, and 2.5 months and imatinib treatment duration – 73, 48, 7, and 13 months correspondingly. Pneumonitis has occurred at months 2, 13, 47 and 48 of imatinib treatment.

Patient	Gender	Age at diagnosis, yrs	CML diagnosis	Start of imatinib	Date of pneumonitis	Imatinib termination	Imatinib treatment duration before pneumonitis, months	Imatinib treatment duration, months
#1	F	13	XI/99	XI/2001	XII/2005	IX/2008	47	73
#2	F	64	XII/02	XI/2004	XI/2008	XI/2008	48	48
#3	F	66	I/08	III/2008	V/2008	XI/2008	2	7
#4	M	40	IX/06	XI/2008	III/2008	III/2008	13	13

Table 1. Characteristics of drug-induced pneumonitis patients.

Here are the case reports of our patients with imatinib-induced pneumonitis. In 2 patients it was revealed after a short, while in another two it was associated with prolonged imatinib treatment. In each case, describes the stages of diagnosis lung disease that emerged while taking imatinib (including retrospective), and treatment.

The first case of drug-induced pneumonitis, a 20 year-old woman, admitted to our center in November, 2007. At age of 13 (in November 1999) the patient was diagnosed with chronic

phase of CML, high-risk group by Sokal on the basis of leukocytosis ($WBC\ 286\times 10^9/L$) with prominent left shift of differential count with 15% blasts, hyperthrombocytosis $2279\times 10^9/L$, spleen +8 cm below costal margin, liver +1 cm below costal margin. It should be noted that under the new WHO classification of 2008, the patient was in accelerated phase CML. The Ph¹-chromosome was found in 100% metaphases. Within two years she was treated with combinations of low-doses ARA-C with hydroxyurea or alpha-interferon (IFN- α), and ARA-C + doxorubicin (7+3). The only result was temporary hematological response without a cytogenetic one. Moreover, the treatment was complicated by avascular necrosis of femoral head. Spleen began to increase gradually, up to 10% of blasts and basophiles (25% or more) was determined in peripheral blood. Since November, 2001 she was taking imatinib (400 mg daily) with restoration of complete hematological response. Despite the absence of cytogenetic response the imatinib dosage was increased to 600 mg daily only at month 32 of treatment. Since December, 2005 (after 11 months at imatinib, 600 mg qd) for another 11 months she also received treatment for suggested disseminated tuberculosis with infiltration and destruction, though it was not confirmed bacteriologically. At the same time the daily imatinib dosage was increased to 800 mg daily because of increasing platelet count (up to $1800\times 10^9/L$). After that she became doing worse with prominent weakness and exertional dyspnea. She has undergone an additional evaluation at Institute of tuberculosis. The CT scan has found multiple confluent areas of alveolar consolidation. The revision of lung biopsy, performed during antituberculosis treatment, revealed mild lymphoid and histiocytic infiltration of bronchioles. She was supposed to have exogenous allergic alveolitis of unknown origin and treated with methylprednisolone (8 mg daily) since May, 2007 along with imatinib. Four months of such treatment has led to further deterioration. The development of pulmonary complications during prolonged high-dose imatinib treatment, ineffectiveness of both antituberculosis drugs and methylprednisolone has allowed suggesting imatinib-induced alveolitis. At September, 2007 imatinib treatment was stopped and the patient has lost hematological response (hyperthrombocytosis, elevating WBC count).

At admission to our center she was complaining of weakness, palpitations, dyspnea at minimal exertion, episodes of chest pain, sense of epigastric pressure, fever (up to $38,5^\circ$) during last 1–2 months, productive cough, pruritus in legs. At physical examination there was only low-grade fever and pigmentation. The chest was deformed because of scoliosis. Lung margins were normal, respiratory rate – 18 breaths per minute, on auscultation the expiratory prolongation (predominantly left-sided) with basilar rales were heard. Heart rate was about 120 bpm, liver and spleen were not enlarged.

The hematological and cytogenetic resistance to imatinib treatment along with suggested non-hematological toxicity (alveolitis) necessitated the additional evaluation and moving the patient to 2nd line TKIs.

The CT scan revealed prominent diffuse bilateral interstitial lung infiltration with honeycomb appearance in upper and middle parts of lungs, along with the focus of lung consolidation in paravertebral part of right S10 without effusion (Figure 1). This was considered as non-specific interstitial pneumonia with supervening infection at right S10.

The bronchoscopy data was normal. The study of bronchoalveolar lavage excluded bacterial overgrowth, PCR analysis has revealed the cytomegalovirus DNA (DNA-CMV). The lavage sediment contained 49% alveolar macrophages, 33% segmented neutrophils, 7% eosinophils, and 11% lymphocytes.

She has undergone the chemotherapy cycle (5+2) along with antibacterial and antiviral drugs; corticosteroids were stopped. The tachycardia (up to 150 bpm), probably due to steroid cardiomyopathy and febrile neutropenia episodes, necessitated the usage of beta-1 blockers (atenolol).

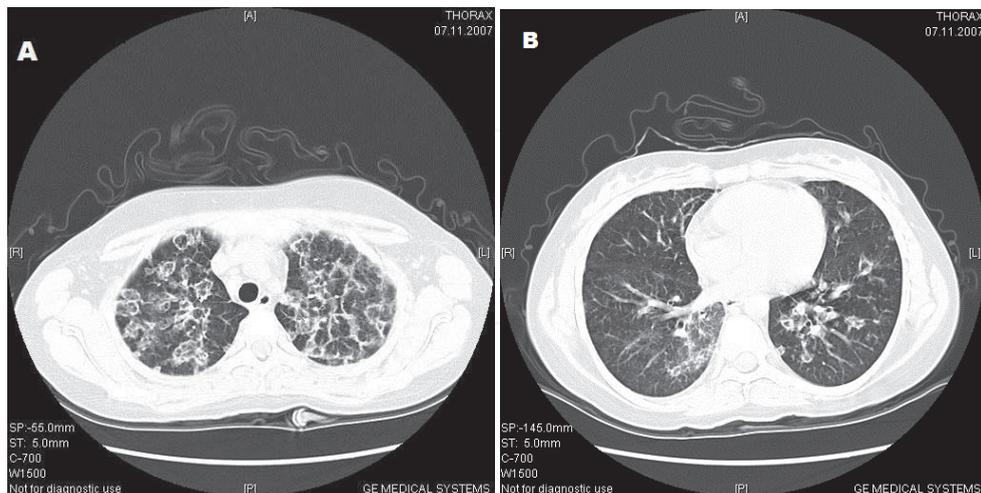


Fig. 1. A, B. Chest CT scan of patient #1 (A – middle, B – lower parts): non-specific interstitial pneumonia with supervened infection.

The serial CT scan showed some regression of interstitial pneumonia with retraction of alveolar infiltration area (against the withdrawal of imatinib). But the infiltrative focus in right lower lobe has enlarged and pleural involvement appeared. The serum galactomannan level was increased to 2,55 ng/ml (normal < 0,5 ng/ml), permitting to diagnose invasive aspergillosis. In addition, the repetitive lavage evaluation has revealed *Enterococcus* spp. growth and HSV-1,2 DNA. We have added antifungal drugs (Amphotericin-B) and modified both antibacterial and antiviral therapy. Thus, the patient noted the multiple pulmonary pathology, which complicates the course of the underlying disease. Therapy has improved the medical condition of the patient: the fever became sub febrile and only few rales could be heard. Since February, 2008 she started treatment with 2nd generation TKI, dasatinib.

At control evaluation (December, 2008) the medical condition of patient was good and stable without any fever. Dasatinib therapy allowed achieving not only complete hematological, but also minor cytogenetic response. The control CT scan picture has shown major improvement with virtually complete regression of interstitial lung infiltration (Fig. 2).

This case demonstrates the development of complex pulmonary disease: **a retrospectively** revealed imatinib-induced pneumonitis after prolonged therapy with imatinib mesylate. Rapid worsening at increased dose of imatinib prompted to reevaluate the previous diagnosis of tuberculosis and to stop imatinib because of suggested exogenous allergic alveolitis. After the resolution of supervened severe pleuropneumonia mixed etiology and lung aspergillosis we became able to start dasatinib treatment with stabilization and improvement of both lung pathology and CML response.

In patient #2, 64 year-old woman, CML chronic phase (high-risk group) was diagnosed in December, 2002. At that moment she was complaining of malaise. There was splenomegaly (+6 cm below costal margin), liver size was normal. The peripheral blood analysis presented hyperleukocytosis ($117 \times 10^9/L$), moderate thrombocytosis ($669 \times 10^9/L$), left shift of differential count. Bone marrow aspirate was hypercellular, karyological examination revealed Ph-chromosome in 100% metaphases. In December, 2002 – November, 2004 she was treated with IFN- α , but achieved only hematological response without cytogenetic one. The next 2 years she was receiving imatinib, 400 mg daily, but didn't achieve major cytogenetic response. Since January, 2007 its dose was increased to 600 mg daily. In August, 2008 she was evaluated for dry cough and dyspnea. There were no rales, or prominent tachypnea (respiration rate 20 per minute) and X-ray didn't find any abnormalities, but persistent complaints have prompted to suspect an imatinib side effect. In November, 2008 the TKI treatment was interrupted.

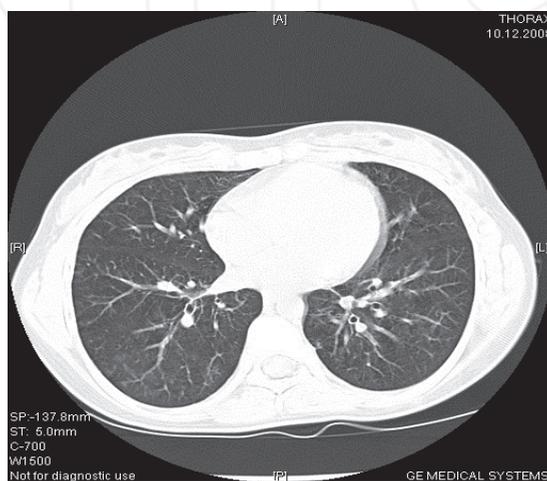


Fig. 2. Control CT scan of patient #1. Nearly complete regression interstitial lung infiltration.

The patient was reevaluated in specialized pulmonologic center. The auscultation revealed basilar crepitation with respiratory rate 22 per minute and SaO_2 97%. Pulmonary function tests showed airflow obstruction (isolated decrease of expiratory flow in distant airways). Static lung volumes were normal and diffusion capacity was moderately decreased. The lung biopsy was not performed. The chest CT scan found interstitial abnormalities with “ground glass” appearance. This data allowed to suggesting drug-induced pneumonitis.

An 8-week prednisolone therapy (25 mg daily) and imatinib interruption has led to significant improvement with resolution of both complaints and CT scan abnormalities. Taking into account the imatinib intolerance (non-hematological toxicity grade 3) and primary cytogenetic resistance, we decided to begin treatment with 2nd generation TKI, nilotinib, 800 mg daily. The nilotinib treatment duration has reached now 24 months. She has achieved a major cytogenetic response (14% bcr/abl-positive cells by FISH). The complaints are absent.

The previous experience helped us to suspect the association of drug-induced pulmonitis with imatinib treatment. Prompt patient evaluation, interruption of imatinib, and quick

response to prednisolone allowed suggesting the development of such a rare complication. Notably, the response to nilotinib underlines the importance of early beginning of 2nd generation TKI treatment in case of primary cytogenetic resistance and imatinib intolerance. Patient #3, 66 year-old woman, was admitted to Hematological Research Center in June, 2008. The diagnosis of high-risk chronic phase CML was established in January, 2008. At diagnosis peripheral blood analysis showed high WBC count ($113 \times 10^9/L$) with left-shifted differential count (blasts – 1%, myelocytes – 11%, metamyelocytes – 6,5%, bands – 24%, segmented – 33,5%, basophils – 8%, eosinophils – 5%, platelets – $849 \times 10^9/L$, Hb 103 g/L). Bone marrow smear showed granulocytic predominance with Ph-chromosome in 98% metaphases. The spleen was +5 cm below costal margin. She also suffered from arterial hypertension, treated with lisinopril. Two months after diagnosis (since 01.03.2008) she began receiving imatinib at standard dose of 400 mg qd. But 2 weeks later she began doing worse and malaise, low-grade fever and progressive dyspnea appeared. Lung auscultation revealed expiratory prolongation without rales. Hemodynamically she was stable. Chest X-ray revealed diffuse interstitial process, confirmed later by CT scan.

The CT scan (Fig. 3) shows diffuse increase of pulmonary vascularity with its deformation by infiltration of intralobular paraseptal interstitium. There were also symmetrical areas of decreased pneumatization with “ground glass” appearance, predominantly in central parts of both lungs. Pleural and pericardial effusions were absent.

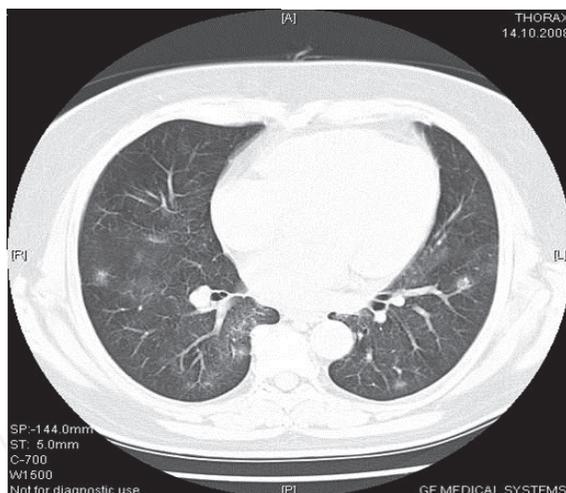


Fig. 3. Chest CT scan with signs of interstitial lung disease (patient #3).

The clinical presentation and CT scan data permitted to suspect these abnormalities to be an imatinib-induced pneumonitis (non-hematological toxicity grade 2). Imatinib was discontinued (since 01.05.2008), and corticosteroids (methylprednisolone, 40 mg daily for 20 days with gradual dose tapering) were started. This therapy has led to significant dyspnea improvement with normalization of temperature and auscultatory findings. CT scan showed the same “ground glass” foci, but their intensity has decreased. The complete resolution of signs and symptoms with delayed resolution of radiological findings after imatinib discontinuation and corticosteroid treatment confirmed the

suggested association of pneumonitis with imatinib treatment. During the treatment interruption (40 days) she has lost the hematological response (WBC – $25 \times 10^9/L$, platelets – $742 \times 10^9/L$). The patient continued treatment with imatinib in decreased dose (300 mg daily) and hypotensive treatment with lisinopril. Two weeks later the hematological response restored. The control caryological examination after 3 months of treatment has confirmed a major cytogenetic response (25% Ph⁺ metaphases). But 2 weeks after the treatment was resumed the dyspnea had relapsed, while control CT scan revealed deterioration (marked increase in size and intensity of previously seen “ground glass” focuses of interstitial infiltration). The increased vascularity was still remaining, along with paraseptal and interlobular interstitial infiltration. These findings once more confirmed the association of pneumonitis with CML treatment. After the imatinib discontinuation she has undergone 16-day methylprednisolone therapy (40 mg daily with gradual tapering). The treatment was discontinued and the hematological response was lost again, necessitating the hydroxyurea treatment (3 g daily).

During 6 months of imatinib treatment this patient achieved optimal response, but it was lost shortly after the treatment interruption (due to toxicity). The non-hematological toxicity (imatinib-induced pneumonitis grade 2), necessitated the treatment swapping to 2nd generation TKIs – nilotinib or dasatinib.

Nilotinib (Tasigna, AMN107, Novartis Pharma AG) is a structural analogue of imatinib. As well as imatinib, it binds ABL-tyrosine kinase in inactive conformation, but is 25–30 times more potent in vitro and active against the majority of its mutated forms (except T315I). Notably it has no cross-resistance with imatinib. Dasatinib (Sprycel, BMS-354825, Bristol Myers Squibb) structurally differs from imatinib. It binds ABL-tyrosine kinase in active conformation and also inhibits SRC-kinases superfamily; by vitro activity it is 300 times more potent, than imatinib and is active against all known mutated forms, except T315I. However, dasatinib should be used cautiously in hypertensive patients. The coexistent arterial hypertension in our patient led us to prefer nilotinib.

At the moment of nilotinib treatment Ph⁺-chromosome was found in 100% metaphases and hematological response was absent too. Now the nilotinib treatment duration is 24 months; she has achieved stable hematological, complete cytogenetic and major molecular response. The control CT scan revealed nearly complete resolution of interstitial lung infiltration and the lung vascularity merely returned to normal pattern. No treatment interruptions needed and the patient noted good drug tolerability.

Concerning the last case (#4) of 40 year-old male we have only a brief information. The diagnosis of chronic phase CML, high-risk group by Sokal was established in September, 2006 (neutrophilic leukocytosis with left-shifted of differential count, hyperthrombocytosis up to $2400 \times 10^9/L$ and Ph⁺-chromosome by karyological examination). Two months later he began successfully taking imatinib (400 mg daily) for a year without side effects. However, in February, 2008 (13th month of treatment) low-grade fever and exertional dyspnea occurred. The evaluation allowed excluding infections. The CT scan has revealed “ground glass” lung abnormalities, with increased and deformed lung vascularity. The patient refused from further evaluation and treatment in specialized center.

This case report is not representative for imatinib-induced pneumonitis. But our goal is to attract attention of physicians to be aware of typical complaints of patients with this pathology and diagnose it earlier.

3. Discussion

The above-mentioned rare disease belongs to a group of interstitial lung diseases, including now more than 150 entries. Despite the etiological differences, including the diseases of unknown origin, all of them involve lung interstitium and its vasculature. This feature underlies their clinical, radiological and pathological similarity.

According to CTC, both interstitial pneumonia and pneumonitis have 5 grades of severity. Grade 1 is asymptomatic and is revealed only radiologically (X-ray, CT scan). Grade 2 is characterized by signs and symptoms, not interfering activities of daily living. Typical clinical presentation along with disturbances of gaseous exchange and activities of daily living indicates a grade 3 pneumonitis. Grade 4 is a life-threatening condition with a need for respiratory support, and death from pneumonitis is considered as 5 grade of toxicity [14].

The pathological examination typically reveals both inflammatory infiltrates and areas of fibrosis. Radiological findings can't be used for differential diagnosis, because they lack specificity and are not only shared within this group, but also could be seen in non-related diseases. **The high-resolution CT scan is more specific and is most useful in serial examinations. Equally important in differential diagnosis are arterial blood gas examination and bronchoscopy with transbronchial biopsies (4–6 specimens) and lavage.** The obtained material should undergo bacteriological, virological and immunological examination.

The mechanism of interstitial lung diseases is complex and has a number of distinctive features. It is thought to be a result of immune complex-mediated reaction with the principal role of T cells and cytokines. The alteration of alveolocytes leads to acute alveolitis. If it doesn't resolve, the inflammation extends to interstitium and its capillaries, leading to pneumosclerosis, alveolar deformation and disturbances of lung diffusion capacity [15].

The treatment of drug-induced pneumonitis consists of avoidance of allergen (here – imatinib) and prednisolone, 1 mg/kg body weight daily, for 2–4 weeks. The dose is then tapered to minimal, sufficient for good results of pulmonary function tests. If contact with allergen is avoided there is no need for continuous corticosteroid treatment [15].

Drug-induced pneumonitis is a rare complication of imatinib treatment in CML patients. In two cases it has developed more than 2 year after the beginning of treatment, despite its good tolerance earlier. In other cases it was revealed at first months of therapy, when good compliance is especially needed for achieving of optimal response. Unfortunately, the complete evaluation (bronchoscopy with transbronchial biopsy and lavage, pulmonary function tests, arterial blood gas examination) was not done in all patients at the time of pneumonitis which is associated with the rare detection of such cases, and often the unwillingness of patients carrying invasive research methods. For example, bronchoscopy with transbronchial biopsy and lavage were performed only in patient #1, the study of blood gases and pulmonary function tests in patient #2. Patients receiving outpatient treatment are often reluctant to conduct invasive research methods. However, the problem of doctors in clinical practice is, in particular, in explaining the importance and need for a comprehensive survey of every obscure case. Its data could elucidate the mechanism of drug-induced pneumonitis development. All of our patients had serial CT scan examination (with the identification of the characteristic CT picture of “ground glass”), the association of interstitial lung disease with imatinib treatment is followed up, and the effectiveness of corticosteroids is estimated.

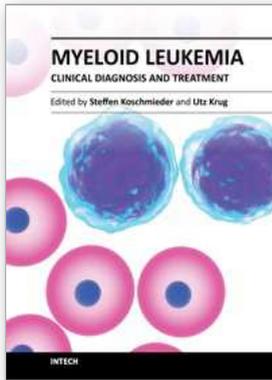
4. Conclusion

These case reports illustrate the importance of search for signs of toxicity at different phases of treatment. Careful searching for adverse events of imatinib in CML patients and differential diagnosis with similar diseases allows prompt diagnosis and treatment of both frequent and rare side effects, including those not in onco- hematology specialist clinics, but also in clinical practice. Proper changing of treatment strategy can help to avoid frequent and prolonged interruptions of treatment due to toxicity and increase the efficacy of treatment, permitting to achieve optimal results.

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This book comprises a series of chapters from experts in the field of diagnosis and treatment of myeloid leukemias from all over the world, including America, Europe, Africa and Asia. It contains both reviews on clinical aspects of acute (AML) and chronic myeloid leukemias (CML) and original publications covering specific clinical aspects of these important diseases. Covering the specifics of myeloid leukemia epidemiology, diagnosis, risk stratification and management by authors from different parts of the world, this book will be of interest to experienced hematologists as well as physicians in training and students from all around the globe.

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