Ocular toxicity with TKI therapy in CML

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Abstract

Tyrosine kinase inhibitors are the standard treatment for Chronic Myeloid Leukemia. They have significantly improved the response rate and global survival in the long term for CML patients, but also added relevant and diverse toxicity. The authors report a clinical case of ocular toxicity connected to the TKIs.

Introduction

Tyrosine kinase inhibitors (TKIs) are highly efficient in the treatment of Chronic Myeloid Leukemia (CML). However, this is usually a lifelong therapy for a great number of patients (only approximately 20% are able to stop this medication safely and permanently). Therefore, adverse events of TKIs are a matter of debate (usually infrequent, manageable and different according to the TKI in use; the most common are muscular pain, fatigue, arthritis, pleural effusions, cardiac toxicity and diarrhea) [1, 2].

Ocular toxicity is classified as a rare adverse event, but also assumed to be underestimated and under-reported [2]. In general, the most common ocular events are periorbital and eyelid edema, erosion of the epithelial surface (keratitis), corneal opacity, blurred vision, periocular pain and conjunctivitis, serous retinal detachment (a rare event; fluid accumulates under the layers of the retina and symptoms include blurred vision, often in both eyes) [3-5]. These events are usually seen in the initial phases of treatment. The decision to reduce dose, hold or discontinue a TKI is complex and should be made after a risk–benefit analysis [2]. The mechanism underlying seems to be connected to the platelet-derived growth factor receptor (PDGFR) and the c-kit marker in mast cells [2]. It was found that the PDGFR is responsible for maintaining the interstitial pressure in the dermis, also expressed in the periocular tissue (as c-kit). TKIs can inhibit these receptors and increased capillary permeability and fluid extravasation [6-7]. The targeting of c-kit–positive mast cells on the conjunctiva can also cause subconjunctival hemorrhage, an event described with Imatinib [6].

The authors report here a case of progressive ocular impairment in a CML patient treated with three different TKIs, raising the issue of ocular toxicity caused by these drugs.

Case Report

A 69-years-old male patient was diagnosed with chronic phase CML, intermediate Sokal and Hasford scores. He had past medical history of hypertension, stroke, iliac artery bypass, syphilis, age-related macular degeneration, syphilitic left eye papillitis (diagnosed 2 years before the CML and treated accordingly with benzathine penicillin), chronic gastritis with angiectasia and prostate benign hyperplasia.

The patient started a first line treatment with Imatinib, which was stopped 14 months later for non-optimal response (he only achieved a morphological response, as shown in the graphic 1) and progressive visual

impairment that begun 3 months after starting the drug. The Ophthalmologist reported the already known non-exudative macular degeneration and papillitis of the left eye, however also found macular edema bilaterally and right eye papillitis. An angiography, thoracic radiography, lumbar puncture, tuberculin test, syphilis, brucella, borrelia and HIV assays were requested, as well as a study for vitamin deficit and a search for auto-imunne diseases. A cerebral CT scan showed no recent abnormality. No organic cause was found for these ophthalmologic disturbs apart from toxicity of imatinib. Oral prednisolone was prescribed (20 mg daily for two weeks, then increased to 60 mg for the papillitis, followed by progressive reduction afterwards) with regression of the edema and the papillitis and minor improvement of the visual deficit.

A second line therapy with Dasatinib 140 mg daily was then prescribed. The patient had a significant reduction of the BCR-ABL transcript but it still remained positive (a morphologic response was obtained once again). The patient complained about the worsening of the visual acuity 4 months after starting the drug. The eye exam allowed the identification of macular edema, the reason for being prescribed prednisolone 20 mg daily for long time, with progressive dose reduction. In the Optical Coherence Tomography (OCT) image there was evidence of reduction of the thickness of both retina (left and right) to 172 ug in the right eye and 183 ug in the left eye. The patient was submitted to phacoemulsification therapy for cataracts in the right eye. Another OCT image was repeated 20 months later showing a continuous progressive reduction of the thickness of both retina, to 162 ug in the right eye and 158 ug in the left eye, in the absence of the external retina and with diffuse atrophy of RPE (retinal pigment epithelium). Dasatinib was stopped three times for anemia (identified to be caused by duodenal angiectasy), with blood transfusions, injectable and oral iron required for long term. The patient also developed a pneumonia with pleural effusion, which was assumed as a typical effect of Dasatinib (stopped 44 months after the first prescription).

Bosutinib 500 mg daily was started as third line therapy. The patient's performance status worsened progressively (with asthenia, dyspnea, worse motor coordination, hyperuricemia, bone pain) mainly between the second and third lines of therapy for the CML). The patient only achieved a complete morphologic response but with the lowest level of the BCR-ABL transcript (ratio BCR-ABL1/ABL1 0,4251 IS). There were also relevant toxicities: two pneumonias (the drug was stopped in both infectious events), grade 2 diarrhea (the drug was stopped for one week, being re-started in reduced dose, progressively mounted until full dose) and worsening of the ocular toxicity. The patient reported worsening of the visual deficit one month after starting the drug, with progressive retinal atrophy (in probable relation with the TKI). Oral prednisolone was re-started (50 mg daily for 2 weeks, with progressive decreasing dose) with no improvement. One month later the retinal atrophy was worse and a macular edema was found (once again assumed to be caused by the TKI). In the OCT image (3 years later) there was an accelerated reduction of the thickness of all layers of both retina, and diffuse absence of the external retina. This TKI was stopped after 16 months of treatment, for the ophthalmologic toxicity in the absence of CML response.

It is important to remember that a major molecular response (MMR) was never achieved with any of the TKIs prescribed, however his symptoms improved and a hematologic response (HR) was obtained, ensuring patient's autonomy. Considering the general state of this patient, the toxicity reported and the absence of optimal response to TKIs, it was decided to prescribe hydroxyurea as a fourth and palliative therapy. There was a stabilization of the hematologic values and the patient's quality of life. The regular control of the BCR-ABL1 transcripts level was stopped for the absence of benefit.

Discussion

The main aim of the TKI therapy is the antileukemic effect that frequently causes manageable adverse events [1]. These events depend on the TKI prescribed, posology, schedule chosen, disease phase, possible interactions with other medications in use and body size [1]. Ocular toxicity has been described as a possible TKI adverse event, usually minor and self-limited. The most common manifestations are papillitis and macular edema. In spite of TKIs having similar mechanisms of action, Imatinib is the most commonly connected to ocular toxicity (periorbital edema can occur in up 70% of the patients); Nilotinib is less reported than Imatinib and Ponatinib, and is rarely described as having this type of adverse events [1, 8, 9, 10, 11]. There is scarce information about Dasatinib and Bosutinib on this subject (there is a case report

of optic neuropathy caused by Dasatinib) [12-15]. Bosutinib is being compared with Imatinib in efficacy and adverse events (ocular toxicity included) for CP-CML (chronic phase) in first line; previous trials did not focus particularly on this toxicity [14-15]. It is advised that a loss of visual acuity should prompt an examination of the optic disc and retina, in order to consider additional systemic steroid therapy and even TKI discontinuation [1].

In order to established a cause-effect relationship between a drug and a secondary effect, we should identify a temporal association, a relationship with the dosage, an improvement after discontinuation (except in cases of continuous aggression for long time, that can cause irreparable damage), a worsening of the symptoms after re-introduction, a possible pathophysiological mechanism, similar effects after introduction of a drug from the same family and the absence of alternative mechanisms that may explain the secondary effect.

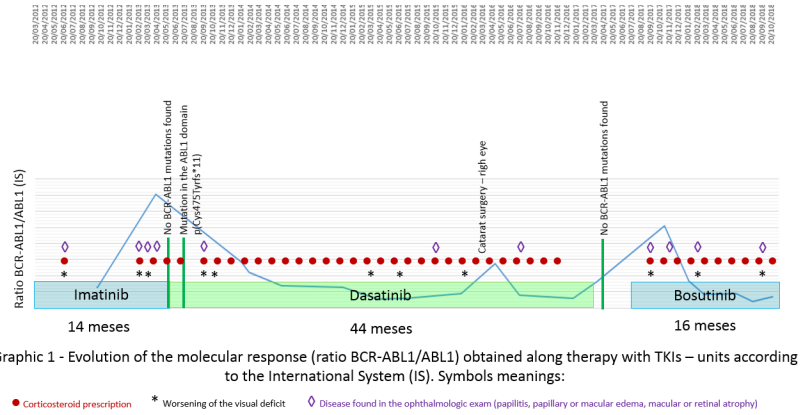
In this particular case report besides having visual defects diagnosed previously to the CML, the old lesions worsened (possibly triggered and accelerated by the TKI) and new deficits were found in the right eye, which begun and persisted along the TKI therapy and worsened in each drug exposure (except the papillitis which was treated). A new and unusual lesion (not described in the literature) is the retinal detachment caused by a macular edema, which persisted in time. There was clinical evidence of toxicity in the ophthalmologic exam and in the OCT exams demanded regularly (irreversible lesions, besides three different treatments with oral corticosteroids). A deeper investigation should be made before assuming toxicity of the drug, as exclusion of an infectious process in peripheral blood and central nervous system (search for active syphilis, HSV, CMV, EBV, ADV, Brucella, Bartonella, HIV, HBV, HCV, HAV; flow cytometry for search of leukemic infiltration), an autoimmune disease (rarely found in older age; antibodies anti-ANA, antiDNA, AntiRO, Anti-La, cANCA, rheumatoid factor) or a vitamin deficit (A, B1, B6, B12, folic acid). A cerebral image as a MRI is relevant for exclusion of infection and malignant infiltration. Evaluation of the main disease (in this clinical case the CML), the past medical history, travels and expositions in daily life are also demanding.

This case confirms the short time between drug exposure and the ocular toxicity and raises the possibility that the visual toxicity identified in this patient might have been a shared event between TKIs (possibly through a common mechanism of action). This can be a limiting factor for the use of these drugs (mainly in older patients with previous ophthalmologic disease). The authors think that an ophthalmologic evaluation before and along TKIs could be a very important surveillance in CML, mainly in patients with previous ophthalmologic disease.

In this specific clinical case, the change of TKI generation was not guided by the ocular toxicity alone (besides the relevant impact in the quality of life of this patient), but also by the absence of optimal response to the last treatment prescribed. However, a better response was never achieved. The treatment was not changed before for the clinical frailty of this patient (age and comorbidities). Only the last TKI achieved a more suitable response compared to the others, but no sufficiently good to ensure an optimal response. In face of an intolerable toxicity in an aged palliative patient (refractory to three generation of TKIs), hydroxyurea was prescribed. This decision improved this patient's quality of life and was enough to control his disease until today.

Conclusion

Permanent visual toxicity can be an adverse event shared between TKIs, possibly through a common mechanism of action, being a limiting factor for the use of these drugs in some cases (mainly in older patients with known ocular deficits). Treatment with corticosteroids did no improvement in this clinical case, as well as the change of TKI therapy. The decision to reduce dose or discontinue a TKI should be made after a risk–benefit analysis.



Graphic 1 - Evolution of the molecular response (ratio BCR-ABL1/ABL1) obtained along therapy with TKIs – units according to the International System (IS). Symbols meanings:

Graphic 1 - Evolution of the BCR-ABL1/ABL1 ratio along the TKI's therapy – units according to the International System (IS) – the time for corticosteroid prescription according to worsening of the visual deficit and ophthalmologic disease reported in regular evaluations.

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