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Chronic myeloid leukemia - Section 6

TKI safety

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Take home messages

- Most side effects of tyrosine kinase inhibitors (TKIs) are reversible and transient, but not necessarily negligible.
- Nilotinib and Ponatinib are very efficacious, but associated with potentially irreversible cardiovascular events, and selection of suitable patients and preventive intervention for these TKIs is key. Dasatinib is associated with pleural effusion which may occur after many years of drug exposure.
- Treat patients efficacy oriented in the early disease phase, and if good responses are achieved one should adopt a more quality-of-life-oriented approach.

Introduction

Chronic myeloid leukemia (CML) patients have excellent prospects to achieve a good response and tolerability with tyrosine kinase inhibitor (TKI) treatment. Independently of which TKI is selected, roughly 5% of patients experience progression, which is difficult to treat.[*1] Reassuringly, about 95% will have a normal life span with similar quality of life (QoL).[2] Upon start of TKI treatment, several aspects are of importance for choice of TKI. Factors such as comorbidities, reimbursement situation, age, QoL, risk score, and the prospect of operational cure (treatment-free remission) may influence choice.[*1] By experience, about 30% to 40% of patients need to switch TKI due to tolerability problems or poor response.[*3]

Side effects of TKIs are mostly mild and reversible, but with longer follow-up some potentially problematic and a few irreversible toxicities have been identified. Cross-intolerance for nonhematological side effects is unusual, that is, the next TKI may be better tolerated than the first. In Europe, we may use imatinib (IM), nilotinib (NIL), dasatinib (DAS), and bosutinib (BOS) in first line and ponatinib in third and later lines, and I will highlight differences and special features of these TKIs. I highly recommend European LeukemiaNet's review of TKI toxicity by Steegman et al.[**4]

Current state of the art

Communal side effects of TKIs

Early hematological toxicity is very common and is probably caused by desired depletion of tumor cells with a poor Ph negative hematopoietic compensatory reserve.[5] Hematological toxicity is more common in advanced and late chronic phase, but properties of the drugs also influence. NIL has least toxicity. NIL < IM < DAS = BOS < PON. Some patients have long-term lower hematological indices during treatment, notably also late-onset macrocytic anemia with high mean corpuscular volume/mean corpuscular hemoglobin in older patients. Hematological toxicity grade 3 lasting more than 2 to 3 months is a warning of a problematic treatment course and poor response.[6] Treatment with growth factors is encouraged to avoid pausing TKI. In practice, short pauses and dose reductions are sometimes necessary (Fig. 1).

Tumor lysis. Surprisingly rare in CML. Patients should drink up to 3 L on a daily basis the first weeks. Allopurinol is not indicated.

Rash. Maculopapular or papulosquamous rash is common with all drugs, most notably NIL. Manage with topical steroids, peroral corticosteroids, and dose interruption. Often the rash does not recur upon rechallenge. If so, a switch of TKI may be considered.

Fluid retention states. Orbital edema is very frequent with IM. Patients should be prewarned about this expected side effect. Excessive lacrimation is frequent. General edema is most common with IM.

Gastrointestinal. Diarrhea, abdominal pain, constipation, vomiting, and nausea are frequent. BOS gives very frequent short-term

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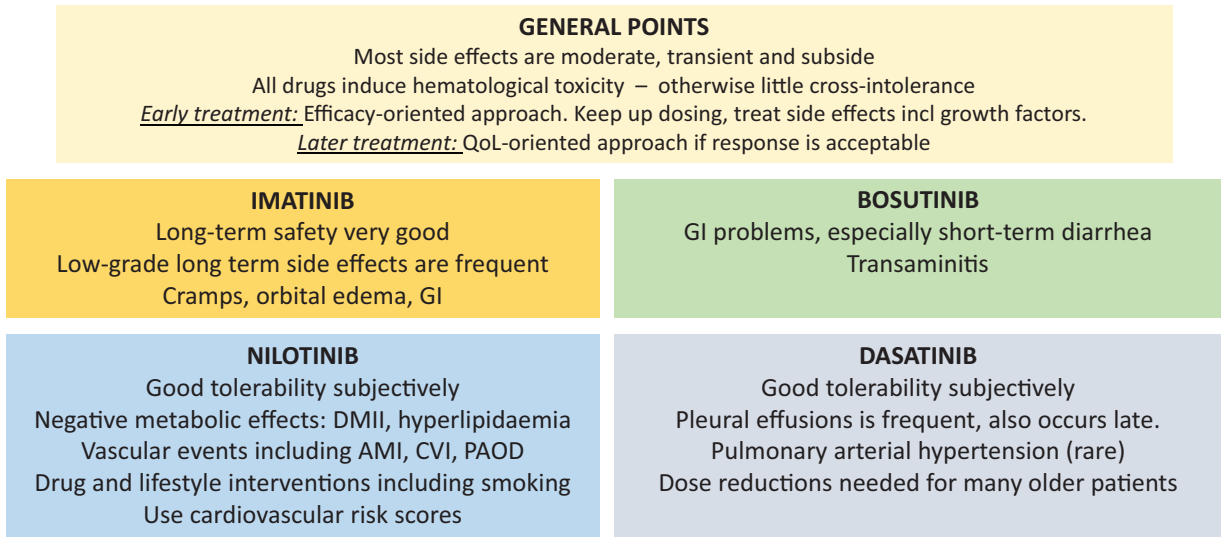

Figure 1. Summary of main points on safety of different tyrosine kinase inhibitors available in first-line treatment. AMI = myocardial infarction, DM2 = diabetes type 2, GI = gastrointestinal, PAOD = peripheral arterial occlusive disease, PCI = percutaneous coronary intervention, QoL = quality of life.

diarrhea which should be proactively managed with loperamide. IM and BOS give most GI problems, NIL and DAS less. To avoid GI problems, BOS and IM should be taken with the largest meal. DAS is meal independent, whereas NIL must be taken in a fasting routine.

Liver and pancreas. Moderate transaminase or pancreatic elevations are not uncommon with TKI treatment. Occurs rarely in DAS and IM treatment, more with NIL, PON, and BOS. This is often transient.

Headache. Most frequent with DAS and NIL but occurs with all drugs.

Musculoskeletal. Ill-defined pains are common with all drugs, with highest frequency for IM. Bothersome cramps are very common with IM. Gentle stretching exercises, quinine or magnesium supplement may be attempted.

Cardiac. QT prolongation is noted, but the practical consequence is unclear.

Potentially irreversible toxicity

Serositis. Most frequently pleural effusions (PEs), but rarely also pericarditis occurs. PE is a troublesome and unpredictable side effect, which may occur years into the treatment course. PE occurs in up to 30% of DAS-treated patients long-term. An incidence of approximately 5% is found with BOS, much rarer for other TKIs. PE is associated with age and may indicate too high dose.[*7] Interruption is recommended, and resolution of PE takes weeks. Pausing is not adverse for efficacy. Some use corticosteroids and diuretics symptomatically, but effect is moderate. Many patients enjoy excellent responses and symptomatic improvement with reinitiation of TKI in lower doses, and anecdotally doses as low as 20 mg daily may still be effective with good tolerability. Recurrence of PE is not infrequent. Fortunately, PE is mostly reversible.

Atherothrombotic and metabolic complications. In the ENESTnd trial, a clear increase of cardiovascular events was noted for NIL versus IM.[*8] Amputations due to accelerated limb atherosclerosis, cerebrovascular, and coronary events were noted. Events most frequently occurred in older patients with metabolic syndrome or preexisting atherosclerosis, but also in patients without known predisposition. The effect was clearly dose-dependent. No increase in mortality has been detected, but this serious and potentially irreversible morbidity has prompted study of cause and recommendations for prevention. NIL and PON adversely change the lipid status and glucose tolerance/diabetes type II. I carefully evaluate cardiovascular risk with risk scores like qRISK and intervene with nonsmoking orders, treat hypertension, hyperlipidemia diabetes type II and give life style advice. Patients who are elderly, have metabolic syndrome, or manifest atherosclerotic disease are not good candidates for NIL. PON gives an even higher incidence of atherothrombosis than NIL and has similar effects on metabolic parameters.[9] PON also raises blood pressure and aggressive treatment (2–3 drugs) is frequently needed. In practice, the only treatment alternative to PON is often allogeneic transplantation, with inherent serious toxicity.[10] Hence, vascular disease prevention is key if PON is used and patients may enjoy good treatment effect and QoL in a difficult clinical situation.

Renal. Reduction in glomerular filtration has been noted by long-term use of IM.

Future perspectives

General advice for management of side effects by TKIs

Side effects are mostly short term and subside with or without symptomatic treatment. Long-term low-grade problems represent a serious threat to efficacy if it affects treatment compliance.[11] The patient and doctor treatment alliance is key. Efficacy considerations are most important early in the treatment course, and the patient's risk of progression may influence management of side effects by more aggressive symptomatic treatment versus pausing/dose reduction. If the patient has good efficacy, I am with time more inclined to dose reduce and pause in attempt achieve good QoL. Rule of thumb: Grade 1: No change. Grade 2: side effects may be managed with symptomatic treatment short-term or pausing. Grade 3: pause drug until Gr 1 and reinitiate at original or lower dose. Grade 4: pause, reinitiate at Gr 1 and dose reduce. If side effects subside I try to increase dose at a later stage, particularly if efficacy is not "optimal" according to guidelines.

References

*1. Hochhaus A, Saussele S, Rosti G, et al. Chronic myeloid leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2017;28 (suppl_4):iv41–iv51.

Newest CML European Guideline.

2. Bower H, Bjorkholm M, Dickman PW, et al. Life expectancy of patients with chronic myeloid leukemia approaches the life expectancy of the general population. *J Clin Oncol.* 2016;34:2851–2857.

*3. de Lavallade H, Apperley JF, Khorashad JS, et al. Imatinib for newly diagnosed patients with chronic myeloid leukemia: incidence of sustained responses in an intention-to-treat analysis. *J Clin Oncol.* 2008;26:3358–3363.

Real-world record of TKI use throughout treatment.

**4. Steegmann JL, Baccarani M, Breccia M, et al. European LeukemiaNet recommendations for the management and avoidance of adverse events of treatment in chronic myeloid leukaemia. *Leukemia.* 2016;30:1648–1671.

The ultimate compilation of TKI safety issues.

5. Mustjoki S, Richter J, Barbany G, et al. Impact of malignant stem cell burden on therapy outcome in newly diagnosed chronic myeloid leukemia patients. *Leukemia.* 2013;27:1520–1526.

6. Milojkovic D, Nicholson E, Apperley JF, et al. Early prediction of success or failure of treatment with second-generation tyrosine kinase inhibitors in patients with chronic myeloid leukemia. *Haematologica.* 2010;95:224–231.

*7. Hughes TP, Laneuville P, Rousselot P, et al. Incidence, outcomes, and risk factors of pleural effusion in patients receiving dasatinib therapy for Philadelphia chromosome-positive leukemia. *Haematologica.* 2019;1:93–101.

Good overview of dasatinib pleural effusions.

*8. Hochhaus A, Saglio G, Hughes TP, et al. Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial. *Leukemia.* 2016;30:1044–1054.

Long-term record of nilotinib safety.

9. Muller MC, Cervantes F, Hjorth-Hansen H, et al. Ponatinib in chronic myeloid leukemia (CML): consensus on patient treatment and management from a European expert panel. *Crit Rev Oncol Hematol.* 2017;120:52–59.

10. Nicolini FE, Basak GW, Kim DW, et al. Overall survival with ponatinib versus allogeneic stem cell transplantation in Philadelphia chromosome-positive leukemias with the T315I mutation. *Cancer.* 2017;123:2875–2880.

11. Marin D, Bazeos A, Mahon FX, et al. Adherence is the critical factor for achieving molecular responses in patients with chronic myeloid leukemia who achieve complete cytogenetic responses on imatinib. *J Clin Oncol.* 2010;28:2381–2388.