Consensus

Expert opinion on the metabolic complications of new anticancer therapies: Tyrosine kinase inhibitors

Avis d'experts sur les complications métaboliques des nouvelles thérapies anti-cancéreuses : inhibiteurs tyrosine kinase

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Abstract

Tyrosine kinase inhibitors (TKI) interfere with glucose metabolism. Contrasting effects have been reported, even for a given molecule. Hyperglycemia rates range between 15 and 40%; nilotinib seems to be the molecule most liable to induce diabetes. Metabolic effects range from metabolic syndrome to onset of diabetes, requiring treatment based on insulin resistance, although pathophysiology is unclear. It is noteworthy that fulminant diabetes has never been reported under TKIs. TKIs may lead to hypoglycemia in type 1 or 2 diabetes. Several cases have been reported of improvement in glycemia and in HbA1c, with reduction or even termination of insulin therapy, mainly under imatinib and sunitinib. Fasting glucose levels should be checked before, during and after treatment, plus HbA1C in diabetic patients, with reinforced self-monitoring. These side-effects are transient and never contraindicate continuation of TKIs. Dyslipidemia under TKI has been reported, concerning both LDL-cholesterol and triglycerides. Although variations seem to be slight, lipid assessment is recommended before, during and after treatment.
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Keywords: Diabetes; Dyslipidemia; Tyrosine kinase inhibitors

Résumé

Les inhibiteurs des tyrosines kinases (ITK) interfèrent avec le métabolisme glucidique. Des effets opposés ont été décrits avec ces thérapies, parfois avec une même molécule. La fréquence des hyperglycémies varient de 15 à 40 %, le nilotinib apparaît être la molécule la plus diabétogène. Ces modifications métaboliques vont du syndrome métabolique à l'apparition d'un diabète, pouvant justifier la mise en place de traitement jouant sur l'insulinorésistance, bien que les explications physiopathologiques restent peu claires. À noter qu'aucun diabète fulminant n'a été décrit sous ITK. Les ITK peuvent exercer un effet hypoglycémiant chez des patients diabétiques de type 1 et 2. Plusieurs cas ont été rapportés avec amélioration des glycémies et de l'HbA1c, réduction, voire arrêt de l'insulinothérapie, essentiellement avec l'imatinib et le sunitinib. La glycémie à jeun devra être contrôlée avant, pendant le traitement et après son arrêt, ainsi que l'HbA1C chez les patients diabétiques, avec une auto-surveillance glycémique renforcée. Ces effets secondaires sont transitoires et ne contre-indiquent, en aucun cas, la poursuite de l'ITK. Des dyslipidémies ont été décrites sous ITK, portant à la fois sur le LDL-cholestérol et les triglycérides. Bien que ces variations semblent minimes, il est recommandé de contrôler un bilan lipidique avant, pendant le traitement et après son arrêt.
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Mots clés : Diabète ; Dyslipidémie ; Inhibiteurs Tyrosine kinase

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1. Glycemia and tyrosine kinase inhibitors: recommendations

R1. TKI treatment can lead to hyperglycemia or hypo-glycemia.

- Diabetes under TKI is diagnosed on two fasting glucose levels > 126 mg/dL (7.0 mmol/L) or any glucose level > 200 mg/dL associated with signs of hyperglycemia.
- Moderate fasting hyperglycemia is defined by a level of 1.1 to 1.26 g/L.
- Glucose levels < 0.7 g/L are considered as hypoglycemia, especially in diabetic patients under treatment.

R2. In case of diabetes under TKI, metformin should be used in first line; due to the risk of malnutrition in the oncologic context, dietary restrictions are not applied strictly. Subsequent treatment follows classic guidelines for non-iatrogenic diabetes, adapted to the HbA1C target.

R3. The HbA1c target in TKI-induced diabetes should be < 8%, personalized according to individual profile and the medical context behind TKI therapy.

R4. Diagnosis of diabetes under TKIs does not contraindicate continuation of treatment. In very rare cases of threatening hyperglycemia, treatment may be interrupted while hyper-glycemia is brought under control, which requires referral to a diabetologist-endocrinologist.

R5. In hypoglycemia under TKI in patients under prior treatment for diabetes, treatment may need to be adapted or interrupted.

R6. Fasting venous glucose should be assessed in non-diabetic patients ahead of initiation of TKI treatment. In case of pre-existing diabetes, good glucose balance needs to be achieved ahead of initiation of TKI treatment (HbA1c assay, with or without glucose monitoring).

R7. In non-diabetic patients, fasting venous glucose should be assessed every 2 weeks during the first month, then monthly throughout TKI treatment. Therapeutic education in signs of hyperglycemia and hypoglycemia should also be ensured.

R8. In moderate fasting hyperglycemia or diabetes prior to initiation of TKI, close glucose self-monitoring and therapeutic education in clinical signs of hyperglycemia and hypoglycemia should be implemented. HbA1c should be assayed every 3 months.

R9. On termination of TKI therapy in patients with moderate fasting hyperglycemia or diabetes, prior to initiation of TKI or not, 4 weeks' glucose self-monitoring is recommended, to adapt antidiabetic treatment.

2. Dyslipidemia and tyrosine kinase inhibitors: recommendations

R1. Lipid targets should be adapted to general health status and individual cardiologic and oncologic prognosis. Current guidelines may be applied in case of good oncologic prognosis; otherwise, less strict targets, based on case-by-case discussion between endocrinologist and oncologist, should be applied, and regularly reassessed according to prognostic progression.

R2. Lipid assessment is to be analyzed in parallel to thyroid assessment, which may be disturbed by TKIs. Any hypothy-roidism should be treated before initiating or intensifying lipid reduction therapy.

R3. Complete lipid work-up (total cholesterol, HDL, LDL, triglycerides) should be performed ahead of TKI therapy.

R4. Lipid assessment should be performed at 3 months then every 6 months during TKI therapy.

R5. At termination of TKI therapy, any lipid reduction therapy should be stopped, with control assessment at 2 months in patients without prior treatment, or reassessment of optimal dose in patients with prior treatment.

3. Glycemia and tyrosine kinase inhibitors

3.1. Epidemiology

Tyrosine kinase inhibitors (TKI) interfere with glucose metabolism. Surprisingly, contrasting effects have been reported, with either hypo- or hyper-glycemia, even for a given molecule.

3.1.1. Hyperglycemia

Clinical studies reported hyperglycemia rates of 15–40%, depending on the molecule.

Iurlo et al. [1] compared the effects of first- and second-generation TKIs on glucose metabolism in chronic myeloid leukemia. Prevalence of diabetes, glucose intolerance and metabolic syndrome did not differ according to TKI molecule; however, glucose profile (fasting glucose, insulinemia, C-peptide, HOMA-IR) was poorer under nilotinib than imatinib or dasatinib.

The most diabetogenic TKI seems to be nilotinib. Under nilotinib, hyperglycemia was reported in 4–38% of patients, according to dose and glucose status prior to therapy, with higher risk in case of pre-diabetes. Episodes were rarely severe: 5% grade 3–4, and glycemia > 2.5 g/L [2–4].

Breccia et al. reported early hyperglycemia under nilotinib, as of the first cycle, in contrast to imatinib [5].

However, Franklin et al., in a large-scale retrospective study of 1272 patients, found shorter mean time to onset of diabetes under dasatinib (3 months) than nilotinib (10.4 months) [6].

Hyperglycemia was equally frequent with other TKIs, but rarely severe, with only 1% severe episodes under pazotinib [7].

The hyperglycemia effect varied according to indication: phase-III clinical trials of sunitinib found hyperglycemia in 15% of patients with metastatic kidney cancer [8], but no glucose abnormalities in digestive stromal or pancreatic tumor [9,10].

No cases of fulminant diabetes have been reported under TKIs (see Table 1).

3.1.2. Hypoglycemia/improvement in diabetes

TKIs can have a hypoglycemic impact in type-1 diabetes as in type-2; several cases have been reported, with improvement in glycemia and HbA1c, with dose-reduction or even termination

Table 1
Frequency of hyperglycemia episodes under TKIs.

TKI	Reference	Type of cancer	*n*	Hyperglycemia (%) All grades	Hyperglycemia (%) Grade 3-4
Nilotinib					
Nilotimib versus imatinib	Saglio [2]	CML	556280	38% 20%	5% 0%
Nilotinib versus controle	Reichardt [57]	GIST	165 83	ND ND	ND ND
Pazotinib					
Pazotinib versus placebo	Sternberg [7]	Kidney	290145	41% 33%	2% 1%
Pazotinib versus placebo	Van der Graaf [58]	Soft-tissue sarcoma	239123	ND ND	ND ND
Sunitinib					
Sunitinib versus interferon α	Motzer [8]	Kidney	375360	15%	
Sunitinib versus placebo	Raymond [9]	Pancreatic NET	83 82	ND ND	ND ND
Sunitinib versus placebo	Demetri [10]	GIST	202102	ND ND	ND ND

Table 2
Cases of improved glucose balance in type-1 diabetes under TKI.

Study	T1 diabetes case	TKI	Indication	Results
Salaroli 2012 [11] Ann Hematol 91, 1823–1824	Male 27 years	Imatinib 400 mg/day	Chronic myeloproliferative disease with TEL-PDGFR β rearrangement	Fall in HbA1c from 7.2% to 5% Onset of symptomatic hypoglycemia episodes Reduced insulin dose
Huda 2014 [12] Diabetes Care, 37, 87–88	Female 48 years	Sunitinib	Gastrin-secreting neuroendocrine tumor	Reduced insulin dose and termination at 3 months' treatment
Templeton 2008 [13] Ann Oncol 19, 824–825	Female 64 years	Sunitinib	Metastatic kidney cancer	Reduced insulin dose and termination at 9 months' treatment

of insulin. Such effects have mainly been reported with imatinib and sunitinib, but also occasionally with other TKIs.

3.1.2.1. Improvement in type-1 diabetes. Three cases have been reported (imatinib, *n* = 1; sunitinib, *n* = 2), with dose-reduction or even termination of insulin therapy shortly after TKI initiation [11–13] (cf. Table 2).

3.1.2.2. Improvement in type-2 diabetes. Data are divergent. A retrospective study of 80 patients, including 17 with diabetes, receiving TKIs (dasatinib, imatinib, sorafenib, sunitinib) reported improved glycemia with reduction or termination of antidiabetic treatment in 8 patients (47%). The "antidiabetic" effect of imatinib persisted after treatment termination, unlike for the other molecules, where termination was accompanied by rebound [14]. Three other studies reported antidiabetic effects of imatinib, with reduction or termination of antidiabetic treatment without change in dietary habits [15–17]. Similar effects were reported under sunitinib [18,19], as well as in isolated cases under dasatinib and erlotinib [20–22]. Other studies found no change in glucose profile under TKIs [23,24] (cf. Table 3).

3.1.2.3. Hypoglycemia in non-diabetic patients. Severe hypoglycemic events were reported in rare cases of non-diabetic patients under sunitinib [25] or imatinib [26,27] (cf. Table 4).

3.2. Pathophysiology

The molecular mechanisms of TKI interference with glucose homeostasis in humans are not fully known [28].

3.2.1. Hyperglycemia

Pathophysiology is unclear, with divergent data: a study of patients with chronic myeloid leukemia treated by nilotinib found reduced insulin secretion (lower urinary C-peptide concentration) [29], while another study of 10 patients found reduced insulin sensitivity on HOMA-IR [30].

3.2.2. Hypoglycemia/improvement in diabetes

The hypoglycemic effect seems to be dependent on the type of TKI, and several pathophysiological hypotheses have been put forward [31,32]:

Table 3
Studies and cases of improved glucose balance in type-2 diabetes under TKI.

Study	T2 diabetes cases	TKI	Indications	Results
Agostino, 2011 [14]	Retrospective 17 patients	Dasatinib 1 Imatinib 6 Sorafenib 5 Sunitinib 7	Multiple	Reduced glycemia and antidiabetic treatment
Veneri, 2005 [15]	Female 70 years	Imatinib 400 mg/day	Myeloid leukemia	Reduction and termination of insulin Correction of glucose load test
Breccia, 2004 [17]	7 patients (3 M, 4F); median age 66 years 3 under insulin 4 under OAD	Imatinib 400 mg/day	Ph+ CML	Reduced antidiabetic treatment from 3 until 12 months' treatment for 6/7 patients
Breccia, 2005 [16]	Female 50 years	Imatinib 400 mg/dayj	Ph+ CML	Reduced glycemia and HbA1C
Oh, 2012 [18]	Retrospective 10 patients	Sunitinib	Metastatic kidney cancer	Improved glycemia, with rebound at TKI termination Treatment termination for 1 patient Reduced treatment for 3 patients
Billemont, 2008 [19]	Retrospective 19 patients inc. 2 under OAD +insulin	Sunitinib 50 mg/day	Metastatic kidney cancer	Reduced glycemia at 4 weeks and treatment termination for 2 patients
Ono, 2012 [20]	Male 57 years	Dasatinib	CML	Reduced insulin dose and 2 weeks' interruption
Breccia, 2008 [22]	Female 66 years	Dasatinib 70mg × 2/j	Ph+ CML	2 hypoglycemia episodes Reduced insulin dose at 2 months' treatment
Costa, 2006 [22]	Female 72 years	Erlotinib 150 mg/day	Non-small-cell lung cancer	At 8 months' treatment, normalization of glycemia and lowered HbA1c

Table 4
Cases of hypoglycemia in non-diabetic patients under TKI.

Study	Non-diabetic cases	TKI	Indication	Results
Lee, 2011 [25] Diabetes Res Clin Pract 93, 68–70	Male 43 years	Sunitinib	Non-functional pancreatic neuroendocrine tumor	Iterative hypoglycemia with 1 severe episode of 1.53 mmol/L
Hamberg, 2006 [26] J Clin Oncol 24, 30–31	Male 57 years Female 52 years	Imatinib	GIST	Hypoglycemic coma and severe hypoglycemia at respectively 2 and 7 weeks after treatment initiation (pro-IGF 2 and IGFBP2 hypersecretion)
Haap, 2006 [27] J Endocrinol Invest 30	Female 62 years	Imatinib	GIST	Severe hypoglycemia (after ruling out differential diagnoses: insulinoma or IGF2 secretion)

- inhibition of tyrosine kinase c-Abl activity by imatinib [33,34], reducing ß-cell apoptosis, increasing ß-cell survival and insulin secretion [35–37];
- inhibition of PDGFR (platelet-derived growth factor receptor) by imatinib, inducing elevation of PPARγ and adiponectin, with protection against insulin resistance [38];
- inhibition of VEGFR2 (vascular endothelial growth factor receptor) by sunitinib, reducing the severity of β-cell inflammation by reducing islet T-cell vascularization and migration [39];
- inhibition of EGFR by erlotinib, enhancing insulin sensitivity by reducing macrophage infiltration of adipose tissue [40];
- other antidiabetic effects of imatimib have been suggested: reduced fibrosis and amyloid deposit affecting β cells in type-2 diabetes [41].

3.3. Diagnosis

No specific symptoms are reported to be associated with onset of these cases of hyperglycemia or hypoglycemia.

The diagnostic criteria for diabetes under TKIs are similar to those for non-iatrogenic diabetes.

Biological diagnosis of diabetes is based on the usual criteria: fasting glucose > 126 mg/dL (7.0 mmol/L) on 2 assays or any glycemia > 200 mg/dL.

Diagnosis of moderate fasting hyperglycemia is based on glycemia between 1.1 and 1.26 g/L [42].

Glycemia < 0.7 g/L in diabetic patients under treatment should be considered as hypoglycemia, and ongoing antidiabetic treatment should be reassessed.

R1. TKI treatment can lead to hyperglycemia or hypoglycemia.

- Diabetes under TKI is diagnosed on two fasting glucose levels > 126 mg/dL (7.0 mmol/L) or any glucose level > 200 mg/dL associated with signs of hyperglycemia.
- Moderate fasting hyperglycemia is defined by a level of 1.1 to 1.26 g/L.
- Glucose levels < 0.7 g/L are considered as hypoglycemia, especially in diabetic patients under treatment.

3.4. Treatment

Treatment of diabetes under TKI is similar to that of non-iatrogenic diabetes. Oncologic prognosis and malnutrition or risk of malnutrition require dietary restrictions to be eased. Physical activity has been shown to be of oncologic benefit, and should be adapted to individual possibilities.

Glycemia elevation is usually progressive, and first-line therapy should target insulin resistance.

The HbA1c target is that recommended by the French Society of Diabetes, taking account of age, life expectancy and comorbidities. In the light of current French guidelines, the target is HbA1c < 8% (for proven severe comorbidity and/or limited life expectancy) [43].

In this context continuing TKI treatment is not contraindicated by onset of hyperglycemia.

In iterative hypoglycemia in diabetic patients under treatment, adaptation may be necessary, with treatment reduced or interrupted according to close glucose monitoring. The opinion of an endocrinologist may be called for.

3.5. Monitoring

3.5.1. Before treatment

Given the increased risk of onset of diabetes in patients with moderate fasting hyperglycemia and the increased risk of

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R2. In case of diabetes under TKI, metformin should be used in first line; due to the risk of malnutrition in the oncologic context, dietary restrictions are not applied strictly. Subsequent treatment follows classic guidelines for non-iatrogenic diabetes, adapted to the HbA1C target.

R3. The HbA1c target in TKI-induced diabetes should be < 8%, personalized according to individual profile and the medical context behind TKI therapy.

R4. Diagnosis of diabetes under TKIs does not contraindicate continuation of treatment. In very rare cases of threatening hyperglycemia, treatment may be interrupted, while hyperglycemia is brought under control, which requires referral to a diabetologist-endocrinologist.

R5. In hypoglycemia under TKI in patients under prior treatment for diabetes, treatment may need to be adapted or interrupted.

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glucose imbalance in diabetic patients, fasting glucose and HbA1c should be assayed before initiating TKI treatment.

This enables early screening for diabetes or pre-diabetes. Patients potentially at risk of type-2 diabetes should be identified, by age, obesity, familial history of type-2 diabetes, and history of gestational diabetes, high blood pressure or dyslipidemia. Nilotinib seems to incur a higher risk of diabetes than other TKIs, and requires particular vigilance.

Conversely, in diabetic patients under treatment, hypoglycemia needs monitoring, as it can be aggravated by TKIs.

R6. Fasting venous glucose should be assessed in non-diabetic patients ahead of initiation of TKI treatment. In case of pre-existing diabetes, good glucose balance needs to be achieved ahead of initiation of TKI treatment (HbA1c assay, with or without glucose monitoring).

3.5.2. During treatment

During treatment, in non-diabetic patients, fasting glucose should be assayed every 2 weeks for the first month of TKI treatment, then monthly.

In patients with diabetes, of whichever type, improved glucose profile has been reported, with episodes of hypoglycemia. Glucose self-monitoring should be reinforced, for adaptation throughout treatment. Glycemia elevation may also occur, and therapeutic education in the clinical signs of hyperglycemia (polyuropolydipsia) and hypoglycemia is indispensable.

R7. In non-diabetic patients, fasting venous glucose should be assessed every 2 weeks during the first month, then monthly throughout TKI treatment. Therapeutic education in signs of hyperglycemia and hypoglycemia should also be ensured.

R8. In moderate fasting hyperglycemia or diabetes prior to initiation of TKI, close glucose self-monitoring and therapeutic education in clinical signs of hyperglycemia and hypoglycemia should be implemented. HbA1c should be assayed every 3 months.

3.5.3. After treatment termination

Glycemic side-effects are usually transient, regressing on termination of treatment, but reversibility should be monitored on post-treatment glucose and HbA1c assay.

R9. On termination of TKI therapy in patients with moderate fasting hyperglycemia or diabetes, prior to initiation of TKI or not, 4 weeks' glucose self-monitoring is recommended, to adapt antidiabetic treatment.

3.6. Predictive factors

As indicated above, the main predictive factors concern the type of TKI, although contrasting effects have been reported even for a given molecule. Pre-diabetes is a risk factor for onset of diabetes under TKI. Glucose elevation under nilotinib has been shown to correlate with body-mass index, which may be predictive of onset of diabetes [44].

4. Dyslipidemia and tyrosine kinase inhibitors

4.1. Epidemiology

Improvement or aggravation of dyslipidemia are related to type of TKI.

Imatinib seems to improve lipid profile. Gottardi et al. [45] reported normalized total cholesterol in 8 out of 9 patients, and normalized triglycerides in 3 of the 4 patients with hypertriglyceridemia at diagnosis. These changes occurred 1 month after initiation of treatment and persisted for several months. Similar results were reported by other teams [46,47].

Song et al. [48], in contrast, reported hyperlipidemia in 85 out of 155 patients (54.9%) under TKIs (sunitinib, pazotinib, sorafenib, famitinib). Dyslipidemia rates for sunitinib, pazotinib, sorafenib and famitinib were respectively 68, 78, 27 and 62%. For one-third of patients total cholesterol was elevated and for one-half triglycerides, with grade-1 hyperlipidemia in 33% of cases, grade II in 18%, and grade III in 4%.

Under nilotinib, the proportion of patients with "non-optimal" LDL-cholesterol increased from 48 to 89% over 6 months, requiring treatment in 22% of cases. Conversely, the proportion of patients with low HDL cholesterol decreased from 40.7 to 7.4% over 6 months [49]. These findings were confirmed by Franklin et al., with higher incidence of dyslipidemia under nilotinib than dasatinib [6]; on the other hand, this difference was not found by Iurlo et al. [1]. Such dyslipidemia is generally well-controlled by statins and reversible on termination of TKI.

Several studies focused on correlations between hypothyroidism and dyslipidemia. Song et al. reported hyperlipidemia under TKIs in 65% of hypothyroid and 42% of euthyroid patients [48]. A 69% rate of dyslipidemia was reported under sunitinib, with 51% of patients also presenting hypothyroidism, although no correlation could be established between the two, as they did not occur at the same intervals or in the same patients [50].

4.2. Pathophysiology

The reasons for imatinib's positive impact on lipid profile are unclear. A protective role was demonstrated in atherosclerosis, probably due to action on PDGF-R [32]. PDGF-R induces phosphorylation of LRP (low-density lipoprotein receptor-related protein), reducing lipotoxicity and increasing peripheral insulin sensitivity [51]. In a murine model of hypercholesterolemia (ApoE-KO) with induced diabetes, imatinib may have prevented onset of atherosclerosis by reducing PDGF-R expression-phosphorylation and expression of presclerotic cytokines, which promote adhesion, migration and proliferation of fibroblasts and endothelial cells [52]. Other mechanisms have been suggested:

- Lepannen [53] showed that imatinib associated to intravascular VEGF-C gene transfer in hypercholesteremic rabbits reduced macrophage migration in atherosclerotic lesions, increased intimal smooth-muscle cell apoptosis and accelerated re-endothelialization;
- Rocha [54] reported reduced viability and proliferation of human aortic smooth-muscle cells under imatinib, suggesting anti-atherosclerosis action.

Conversely, nilotinib was associated with increased risk of obliterating vascular disease, by aggravating cardiovascular risk factors, including LDL-cholesterol elevation [55].

Pathophysiology at present remains unclear.

4.3. Diagnosis and treatment

Diagnosis of dyslipidemia under TKIs is similar to that of non-iatrogenic dyslipidemia. Thresholds and target levels are defined by general health status, prognosis, and cardiovascular history and risk factors. Control of cardiovascular risk factors needs to be discussed for patients in short- or medium-term life-threatening situations. Current guidelines may be applied in case of good oncologic prognosis [56].

As indicated above, lipid profile should be assessed in parallel to thyroid profile, as TKIs induce hypothyroidism liable to alter the former.

Reported changes in lipid profile are usually mild.

In some cases of dyslipidemia under TKI, however, hygiene and dietary rules or transitional treatment may be applied.

R1. Lipid targets should be adapted to general health status and individual cardiologic and oncologic prognosis. Current guidelines may be applied in case of good oncologic prognosis; otherwise, less strict targets, based on case-by-case discussion between endocrinologist and oncologist, should be applied, and regularly reassessed according to prognostic progression.

R2. Lipid assessment is to be analyzed in parallel to thyroid assessment, which may be disturbed by TKIs. Any hypothyroidism should be treated before initiating or intensifying lipid reduction therapy.

4.4. Monitoring

As lipid profile is impaired by most TKIs, pre-treatment assessment is necessary, with 3 months' monitoring after TKI initiation, then every 6 months. Such dyslipidemia is reversible on termination of TKI.

R3. Complete lipid work-up (total cholesterol, HDL, LDL, triglycerides) should be performed ahead of TKI therapy.

R4. Lipid assessment should be performed at 3 months then every 6 months during TKI therapy.

R5. At termination of TKI therapy, any lipid reduction therapy should be stopped, with control assessment at 2 months in patients without prior treatment, or reassessment of optimal dose in patients with prior treatment.

4.5. Predictive factors

No predictive factors have been identified for onset of dyslipidemia under TKIs.

Disclosure of interest

The authors declare that they have no competing interest.

References

[1] Iurlo A, Orsi E, Cattaneo D, Resi V, Bucelli C, Orofino N, et al. Effects of first- and second-generation tyrosine kinase inhibitor therapy on glucose and lipid metabolism in chronic myeloid leukemia patients: a real clinical problem? Oncotarget 2015;6:33944–51.

[2] Saglio G, Kim D-W, Issaragrisil S, le Coutre P, Etienne G, Lobo C, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med 2010;362:2251–9.

[3] Kantarjian HM, Hochhaus A, Saglio G, De Souza C, Flinn IW, Stenke L, et al. Nilotinib versus imatinib for the treatment of patients with newly diagnosed chronic phase, Philadelphia chromosome-positive, chronic myeloid leukaemia: 24-month minimum follow-up of the phase 3 randomised ENESTnd trial. Lancet Oncol 2011;12:841–51.

[4] Hochhaus A, Saglio G, Hughes TP, Larson RA, Kim D-W, Issaragrisil S, 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;30:1044–54.

[5] Breccia M, Muscaritoli M, Gentilini F, Latagliata R, Carmosino I, Rossi Fanelli F, et al. Impaired fasting glucose level as metabolic side effect of nilotinib in non-diabetic chronic myeloid leukemia patients resistant to imatinib. Leuk Res 2007;31:1770–2.

[6] Franklin M, Burns L, Perez S, Yerragolam D, Makenbaeva D. Incidence of type 2 diabetes mellitus and hyperlipidemia in patients prescribed dasatinib or nilotinib as first- or second-line therapy for chronic myelogenous leukemia in the US. Curr Med Res Opin 2018;34:353–60.

[7] Sternberg CN, Davis ID, Mardiak J, Szczylik C, Lee E, Wagstaff J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol 2010;28:1061–8.

[8] Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 2007;356:115–24.

[9] Raymond E, Dahan L, Raoul J-L, Bang Y-J, Borbath I, Lombard-Bohas C, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med 2011;364:501–13.

[10] Demetri GD, van Oosterom AT, Garrett CR, Blackstein ME, Shah MH, Verweij J, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet 2006;368:1329–38.

[11] Salaroli A, Loglisci G, Serrao A, Alimena G, Breccia M. Fasting glucose level reduction induced by imatinib in chronic myeloproliferative disease with TEL-PDGFRβ rearrangement and type 1 diabetes. Ann Hematol 2012;91:1823–4.

[12] Huda MSB, Amiel SA, Ross P, Aylwin SJB. Tyrosine kinase inhibitor sunitinib allows insulin independence in long-standing type 1 diabetes. Diabetes Care 2014;37:e87–8.

[13] Templeton A, Brändle M, Cerny T, Gillessen S. Remission of diabetes while on sunitinib treatment for renal cell carcinoma. Ann Oncol 2008;19:824–5.

[14] Agostino NM, Chinchilli VM, Lynch CJ, Koszyk-Szewczyk A, Gingrich R, Sivik J, et al. Effect of the tyrosine kinase inhibitors (sunitinib, sorafenib, dasatinib, and imatinib) on blood glucose levels in diabetic and nondiabetic patients in general clinical practice. J Oncol Pharm Pract 2011;17:197–202.

[15] Veneri D, Franchini M, Bonora E. Imatinib and regression of type 2 diabetes. N Engl J Med 2005;352:1049–50.

[16] Breccia M, Muscaritoli M, Alimena G. Reduction of glycosylated hemoglobin with stable insulin levels in a diabetic patient with chronic myeloid leukemia responsive to imatinib. Haematologica 2005;90. ECR21.

[17] Breccia M, Muscaritoli M, Aversa Z, Mandelli F, Alimena G. Imatinib mesylate may improve fasting blood glucose in diabetic Ph+ chronic myelogenous leukemia patients responsive to treatment. J Clin Oncol 2004;22:4653–5.

[18] Oh JJ, Hong SK, Joo YM, Lee BK, Min SH, Lee S, et al. Impact of sunitinib treatment on blood glucose levels in patients with metastatic renal cell carcinoma. Jpn J Clin Oncol 2012;42:314–7.

[19] Billemont B, Medioni J, Taillade L, Helley D, Meric JB, Rixe O, et al. Blood glucose levels in patients with metastatic renal cell carcinoma treated with sunitinib. Br J Cancer 2008;99:1380–2.

[20] Ono K, Suzushima H, Watanabe Y, Kikukawa Y, Shimomura T, Furukawa N, et al. Rapid amelioration of hyperglycemia facilitated by dasatinib in a chronic myeloid leukemia patient with type 2 diabetes mellitus. Intern Med Tokyo Jpn 2012;51:2763–6.

[21] Breccia M, Muscaritoli M, Cannella L, Stefanizzi C, Frustaci A, Alimena G. Fasting glucose improvement under dasatinib treatment in an accelerated phase chronic myeloid leukemia patient unresponsive to imatinib and nilotinib. Leuk Res 2008;32:1626–8.

[22] Costa DB, Huberman MS. Improvement of type 2 diabetes in a lung cancer patient treated with Erlotinib. Diabetes Care 2006;29:1711.

[23] Dingli D, Wolf RC, Vella A. Imatinib and type 2 diabetes. Endocr Pract 2007;13:126–30.

[24] Mariani S, Tornaghi L, Sassone M, Basciani S, Buzzetti R, Gambacorti-Passerini C, et al. Imatinib does not substantially modify the glycemic profile in patients with chronic myeloid leukaemia. Leuk Res 2010;34:e5–7.

[25] Lee Y, Jung HS, Choi HJ, Kim MJ, Kim TM, Park KS, et al. Life-threatening hypoglycemia induced by a tyrosine kinase inhibitor in a patient with neuroendocrine tumor: a case report. Diabetes Res Clin Pract 2011;93:e68–70.

[26] Hamberg P, de Jong FA, Boonstra JG, van Doorn J, Verweij J, Sleijfer S. Non-islet-cell tumor induced hypoglycemia in patients with advanced gastrointestinal stromal tumor possibly worsened by imatinib. J Clin Oncol 2006;24:e30–1.

[27] Haap M, Gallwitz B, Thamer C, Müssig K, Häring H-U, Kanz L, et al. Symptomatic hypoglycemia during imatinib mesylate in a non-diabetic female patient with gastrointestinal stromal tumor. J Endocrinol Invest 2007;30:688–92.

[28] Breccia M, Molica M, Alimena G. How tyrosine kinase inhibitors impair metabolism and endocrine system function: a systematic updated review. Leuk Res 2014;38:1392–8.

[29] Ito Y, Miyamoto T, Chong Y, Maki T, Akashi K, Kamimura T. Nilotinib exacerbates diabetes mellitus by decreasing secretion of endogenous insulin. Int J Hematol 2013;97:135–8.

[30] Racil Z, Razga F, Drapalova J, Buresova L, Zackova D, Palackova M, et al. Mechanism of impaired glucose metabolism during nilotinib therapy in patients with chronic myelogenous leukemia. Haematologica 2013;98:e124–6.

[31] Fountas A, Diamantopoulos L-N, Tsatsoulis A. Tyrosine kinase inhibitors and diabetes: a novel treatment paradigm? Trends Endocrinol Metab 2015;26:643–56.

[32] Breccia M, Alimena G. The metabolic consequences of imatinib mesylate: changes on glucose, lypidic and bone metabolism. Leuk Res 2009;33:871–5.

[33] Hägerkvist R, Sandler S, Mokhtari D, Welsh N. Amelioration of diabetes by imatinib mesylate (Gleevec): role of beta-cell NF-kappaB activation and anti-apoptotic preconditioning. FASEB 2007;21:618–28.

[34] Karunakaran U, Park SJ, Jun DY, Sim T, Park K-G, Kim MO, et al. Non-receptor tyrosine kinase inhibitors enhances β-cell survival by suppressing the PKCδ signal transduction pathway in streptozotocin-induced β-cell apoptosis. Cell Signal 2015;27:1066–74.

[35] Xia C-Q, Zhang P, Li S, Yuan L, Xia T, Xie C, et al. C-Abl inhibitor imatinib enhances insulin production by β cells: c-Abl negatively regulates insulin production via interfering with the expression of NKx2.2 and GLUT-2. PloS One 2014;9:e97694.

[36] Mokhtari D, Al-Amin A, Turpaev K, Li T, Idevall-Hagren O, Li J, et al. Imatinib mesilate-induced phosphatidylinositol 3-kinase signalling and improved survival in insulin-producing cells: role of Src homology 2-containing inositol 5′-phosphatase interaction with c-Abl. Diabetologia 2013;56:1327–38.

[37] Fred RG, Boddeti SK, Lundberg M, Welsh N. Imatinib mesylate stimulates low-density lipoprotein receptor-related protein 1-mediated ERK phosphorylation in insulin-producing cells. Clin Sci 2015;128:17–28.

[38] Fitter S, Vandyke K, Schultz CG, White D, Hughes TP, Zannettino ACW. Plasma adiponectin levels are markedly elevated in imatinib-treated chronic myeloid leukemia (CML) patients: a mechanism for improved insulin sensitivity in type 2 diabetic CML patients? J Clin Endocrinol Metab 2010;95:3763–7.

[39] Villalta SA, Lang J, Kubeck S, Kabre B, Szot GL, Calderon B, et al. Inhibition of VEGFR-2 reverses type 1 diabetes in NOD mice by abrogating insulitis and restoring islet function. Diabetes 2013;62:2870–8.

[40] Prada PO, Ropelle ER, Mourão RH, de Souza CT, Pauli JR, Cintra DE, et al. EGFR tyrosine kinase inhibitor (PD153035) improves glucose tolerance and insulin action in high-fat diet-fed mice. Diabetes 2009;58:2910–9.

[41] Welsh N. Does the small tyrosine kinase inhibitor Imatinib mesylate counteract diabetes by affecting pancreatic islet amyloidosis and fibrosis? Expert Opin Investig Drugs 2012;21:1743–50.

[42] Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 1998;15:539–53.

[43] Darmon P, Bauduceau B, Bordier L, Bringer J, Chabrier G, Charbonnel B, et al. Prise de position de la Société Francophone du Diabète (SFD) sur la prise en charge médicamenteuse de l'hyperglycémie du patient diabétique de type 2. Med Mal Metab 2017:6.

[44] Breccia M, Loglisci G, Salaroli A, Serrao A, Alimena G. Nilotinib-mediated increase in fasting glucose level is reversible, does not convert to type 2 diabetes and is likely correlated with increased body mass index. Leuk Res 2012;36:e66–7.

[45] Gottardi M, Manzato E, Gherlinzoni F. Imatinib and hyperlipidemia. N Engl J Med 2005;353:2722–3.

[46] Franceschino A, Tornaghi L, Benemacher V, Assouline S, Gambacorti-Passerini C. Alterations in creatine kinase, phosphate and lipid values in patients with chronic myeloid leukemia during treatment with imatinib. Haematologica 2008;93:317–8.

[47] Gologan R, Constantinescu G, Georgescu D, Ostroveanu D, Vasilache D, Dobrea C, et al. Hypolipemiant besides antileukemic effect of imatinib mesylate. Leuk Res 2009;33:1285–7.

[48] Song Y, Du C, Zhang W, Sun Y, Yang L, Cui C, et al. A study on the association between hyperlipidemia and hypothyroidism and the response to TKIs in metastatic renal cell carcinoma. Asia Pac J Clin Oncol 2016;12:174–80.

[49] Rea D, Mirault T, Cluzeau T, Gautier J-F, Guilhot F, Dombret H, et al. Early onset hypercholesterolemia induced by the 2nd-generation tyrosine kinase inhibitor nilotinib in patients with chronic phase-chronic myeloid leukemia. Haematologica 2014;99:1197–203.

[50] Tassi R, Baldazzi V, Lapini A, Carini M, Mazzanti R. Hyperlipidemia and hypothyroidism among metastatic renal cell carcinoma patients taking sunitinib malate. Related or unrelated adverse events? Clin Genitourin Cancer 2015;13:e101–5.

[51] Boucher P, Gotthardt M, Li W-P, Anderson RGW, Herz J. LRP: role in vascular wall integrity and protection from atherosclerosis. Science 2003;300:329–32.

[52] Lassila M, Allen TJ, Cao Z, Thallas V, Jandeleit-Dahm KA, Candido R, et al. Imatinib attenuates diabetes-associated atherosclerosis. Arterioscler Thromb Vasc Biol 2004;24:935–42.

[53] Leppänen O, Rutanen J, Hiltunen MO, Rissanen TT, Turunen MP, Sjöblom T, et al. Oral imatinib mesylate (STI571/gleevec) improves the efficacy of local intravascular vascular endothelial growth factor-C gene transfer in reducing neointimal growth in hypercholesterolemic rabbits. Circulation 2004;109:1140–6.

[54] Rocha A, Azevedo I, Soares R. Anti-angiogenic effects of imatinib target smooth muscle cells but not endothelial cells. Angiogenesis 2007;10:279–86.

[55] Kim TD, Rea D, Schwarz M, Grille P, Nicolini FE, Rosti G, et al. Peripheral artery occlusive disease in chronic phase chronic myeloid leukemia patients treated with nilotinib or imatinib. Leukemia 2013;27:1316–21.

[56] French Society of Endocrinology (SFE), Francophone Society of Diabetes (SFD), New French Society of Atherosclerosis (NSFA)Béliard S, Bonnet F, Bouhanick B, et al. Consensus statement on the management of dyslipidaemias in adults. Ann Endocrinol 2017;78:43–53.

[57] Reichardt P, Blay J-Y, Gelderblom H, Schlemmer M, Demetri GD, Bui-Nguyen B, et al. Phase III study of nilotinib versus best supportive care with or without a TKI in patients with gastrointestinal stromal tumors resistant to or intolerant of imatinib and sunitinib. Ann Oncol 2012;23:1680–7.

[58] van der Graaf WTA, Blay J-Y, Chawla SP, Kim D-W, Bui-Nguyen B, Casali PG, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2012;379:1879–86.