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 tyrosoine 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 glyceremia 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 apparaîtrait 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 Tyrosoine kinase

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1. Glycemia and tyrosine kinase inhibitors: recommendations

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.

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.

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 hypothyroidism 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 pazopinib [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).
3.1.2.2. 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 glycaemia 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).

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

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

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.

<table>
<thead>
<tr>
<th>Study</th>
<th>T2 diabetes cases</th>
<th>TKI</th>
<th>Indications</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agostino, 2011</td>
<td>Retrospective 17 patients</td>
<td>Dasatinib 1</td>
<td>Multiple</td>
<td>Reduced glycermia and antidiabetic treatment</td>
</tr>
<tr>
<td>Veneri, 2005</td>
<td>Female 70 years</td>
<td>Imatinib 400 mg/day</td>
<td>Myeloid leukemia</td>
<td>Reduction and termination of insulin</td>
</tr>
<tr>
<td>Breccia, 2004</td>
<td>7 patients (3M, 4F); median age 66 years</td>
<td>Imatinib 400 mg/day</td>
<td>Ph+ CML</td>
<td>Reduced antidiabetic treatment from 3 until 12 months’ treatment for 67 patients</td>
</tr>
<tr>
<td>Breccia, 2005</td>
<td>Female 50 years</td>
<td>Imatinib 400 mg/dayj</td>
<td>Ph+ CML</td>
<td>Reduced glycermia and HbA1C</td>
</tr>
<tr>
<td>Oh, 2012</td>
<td>Retrospective 10 patients</td>
<td>Sunitinib</td>
<td>Metastatic kidney cancer</td>
<td>Improved glycermia, with rebound at TKI termination</td>
</tr>
<tr>
<td>Billemont, 2008</td>
<td>Retrospective 19 patients inc. 2 under OAD +insulin</td>
<td>Sunitinib 50 mg/day</td>
<td>Metastatic kidney cancer</td>
<td>Reduced glycermia at 4 weeks and treatment termination for 2 patients</td>
</tr>
<tr>
<td>Ono, 2012</td>
<td>Male 57 years</td>
<td>Dasatinib</td>
<td>CML</td>
<td>Reduced insulin dose and 2 weeks’ interruption</td>
</tr>
<tr>
<td>Breccia, 2008</td>
<td>Female 66 years</td>
<td>Dasatinib 70mg × 2/j</td>
<td>Ph+ CML</td>
<td>Reduced insulin dose at 2 months’ treatment</td>
</tr>
<tr>
<td>Costa, 2006</td>
<td>Female 72 years</td>
<td>Erlotinib 150 mg/day</td>
<td>Non-small-cell lung cancer</td>
<td>At 8 months’ treatment, normalization of glycermia and lowered HbA1c</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Non-diabetic cases</th>
<th>TKI</th>
<th>Indication</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee, 2011</td>
<td>Male 43 years</td>
<td>Sunitinib</td>
<td>Non-functional pancreatic neuroendocrine tumor</td>
<td>Iterative hypoglycemia with 1 severe episode of 1.53 mmol/L</td>
</tr>
<tr>
<td>Hamberg, 2006</td>
<td>Male 57 years</td>
<td>Imatinib</td>
<td>GIST</td>
<td>Hypoglycemic coma and severe hypoglycemia at respectively 2 and 7 weeks after treatment initiation (pro-IGF 2 and IGFBP2 hypersecretion)</td>
</tr>
<tr>
<td>J Clin Oncol 24, 30–31</td>
<td>Female 52 years</td>
<td>Imatinib</td>
<td>GIST</td>
<td>Severe hypoglycemia (after ruling out differential diagnoses: insulinoma or IGF2 secretion)</td>
</tr>
<tr>
<td>Haap, 2006</td>
<td>Female 62 years</td>
<td>Imatinib</td>
<td>GIST</td>
<td>Severe hypoglycemia (after ruling out differential diagnoses: insulinoma or IGF2 secretion)</td>
</tr>
</tbody>
</table>

- inhibition of tyrosine kinase c-Abl activity by imatinib [33,34], reducing β-cell apoptosis, increasing β-cell survival and insulin secretion [35–37];
- inhibition of PDGFR (platelet-derived growth factor receptor) by imatinib, inducing elevation of PPAR-γ 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 imatinib 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 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.

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.

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 (polyuric polydipsia) and hypoglycemia is indispensable.
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.

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.

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 hypertriglyceridermia 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, farnitnib). Dyslipidemia rates for sunitinib, pazotinib, sorafenib and farnitnib were respectively 68, 78, 27 and 62%. For one-third of patients total cholesterol was elevated and for one-half triglycerides, with grade-I 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 Jurlo 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 cardiological and oncological prognosis. Current guidelines may be applied in case of good oncological 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


