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REVIEW ARTICLE

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Side effects of tyrosine kinase inhibitors — management guidelines

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ABSTRACT

Tyrosine kinase inhibitors (TKI) are molecular targeted therapies that inhibit EGFR-related signal transduction pathway. Non-small cell lung cancer patients harbouring activating mutation benefit more from EGFR TKI in first line treatment than from standard platinum-based chemotherapy in terms of objective response rate, quality of life, progression free survival and, in some cases, overall survival. Treatment-related adverse events are observed in 70 per cent of patients but mainly in mild or moderate grade. The most common adverse events are: skin disorders, fatigue, diarrhoea, and elevated liver enzymes. Rare cases of interstitial lung disease are also observed. In clinical practice the treatment plan is achieved and drug discontinuation is rarely needed provided that the guidelines of prevention and management of the toxicities are followed.

Key words: tyrosine kinase inhibitors, adverse events, toxicity, management

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Introduction

Tyrosine kinase (TK) is an enzyme localised both in the cellular cytoplasm (non-receptor tyrosine kinase) and on the intracellular domain of the receptor (receptor tyrosine kinase). TK catalyses the transfer of the phosphate group from the 5'-adenonsine triphosphate to the target protein, which triggers further activation of the signal transduction into the cellular cytoplasm. The deregulation of the TK activity, which — amongst other things — results from the mutation of the epidermal growth factor gene (EGFR), plays a pathogenic role in some malignancies. Small molecule intracellular tyrosine kinase inhibitors (TKI) belong to the group of the molecularly targeted agents that inhibit the transduction of the intracellular signal from the EGFR.

In patients with non-small cell lung cancer (NSCLC) harbouring activating mutation of the *EGFR* gene (most frequently within exon 19 or a single-point mutation within exon 21) promoting the achievement of the response to the TKI, molecularly targeted agents are considered the standard first-line treatment. Compared to traditional chemotherapy regimens based on the platinum derivate, TKI provides better objective response rate, better quality of life, improved progression-free survival, and in some patients prolonged overall survival. Among the patients with advance NSCLC and the presence of the predictive marker, receiving TKI EGFR, we can observe overall survival exceeding 20 months [1]. The most frequently used drugs from the aforementioned group are the reversible inhibitors — erlotinib and gefitinib — as well as a second-generation TKI inhibitor — afatinib — which provides an irreversible blockade of the signalling axe from the EGFR, HER2, and HER4 receptor.

A mechanism of action different from the traditional chemotherapy results in a distinct toxicity profile. Treatment-related side effects of various intensities are observed in 70% of patients [2–4]. The side effects characteristic for the classic chemotherapy (e.g. nausea, vomiting, myelosuppression) are significantly rarer. The most common side effects are skin changes, weakness, diarrhoea, and hepatotoxicity. The majority of the side effects are observed in a mild or moderate grade and are reversible. A rare but potentially fatal side effect of TKI therapy is interstitial lung disease (ILD).

Table 1. CTCAE skin toxicity grading [8]

Grade	Symptoms
1	Papules or pustules, covering less than 10% of body surface area, which may or may not be associated with symptoms of pruritus or tenderness
2	Papules or pustules, covering 10–30% of body surface area, which may or may not be associated with symptoms of pruritus or tenderness Limited impact on daily living
3	Papules or pustules, covering more than 30% of body surface area, which may or may not be associated with symptoms of pruritus or tenderness Limits self-care activities of daily living Associated with local superinfection, with oral antibiotics indicated
4	Papules or pustules, covering any percentage of body surface area, which may or may not be associated with symptoms of pruritus or tenderness, and which are associated with extensive superinfection, with intravenous antibiotics indicated Life-threatening consequences
5	Death

CTCAE — Common Toxicity Criteria for Adverse Events

Dermatologic toxicity

Pathogenesis

In physiological conditions the EGFR receptors are localised within the basement membrane of the dermis, within the epithelial cells of the hair follicles, sweat and sebaceous glands, and within the corneal epithelium and the eyelid. They play an important role in the normal growth and differentiation of the keratinocytes. The blockade of their function due the inhibition of the intracellular signal transduction stops the growth, migration, and proliferation of the cell, and turns it towards the apoptotic pathway. The differentiation and maturation of the skin cells is disturbed, the production of the pro-inflammatory chemokines is stimulated, and as a consequence the dermis structure is changed, the skin thins, and the epithelium is impaired [5]. The impact of the TKI EGFR on the secretion of the pro-inflammatory chemokines promotes the migration of the pro-inflammatory cells and the infiltration of the hair follicles. The most common dermatologic side effects during the TKI EGFR treatment are acne-like (acneiform) rash, dryness and hyperkeratosis of the skin, discoloration, perifollicular inflammation, and changes in the structure of the lashes, hair, and nails. In the latter stage, if no appropriate local treatment is applied, the skin changes may become superinfected by the bacteria and require antibiotherapy.

Incidence

The most common localisation of the skin side effects of the TKI EGFR therapy is the head and trunk area. According to the data from the clinical trials more than 70% of patients treated with the TKI EGFR experience skin side effects [6]. The skin toxicity appears as early as two weeks into treatment with TKI EGFR and may spontaneously regress or escalate during the treatment [7]. A skin toxicity of grade 3 or higher, evaluated with the toxicity CTCAE evaluation scale, 4th version (Common Toxicity for Adverse Events), is observed in 2–16% of patients, and its incidence is comparable in the groups treated with the reversible and irreversible TKI (Table 1).

Table 2. Management of the dermatologic toxicity

CTCAE Grade	Management
1	No treatment or Topical hydrocortisone and/or clindamycin Continue TKI EGFR at the current dose
2	Topical hydrocortisone and/or clindamycin + oral antibiotic from the tetracycline group Continue TKI EGFR at the current dose
3 or 4	Local treatment + oral antibiotic from the tetracycline group + methylprednisolone orally TKI dose interruption until regression of the toxicity to grade 1

CTCAE — Common Toxicity Criteria for Adverse Events

Management

The management depends on the intensity of the skin side effects (Table 2). The CTCAE toxicity grading scale does not include the duration of the symptoms. Long-lasting skin toxicity — even of the mild grade — may influence the subjective feelings and the quality of life of the patients [8]. To decrease the risk of develop-

ing the bothersome symptoms due to the skin changes related to the TKI EGFR treatment, the patient should receive recommendations concerning the appropriate skin care. During the treatment sun exposure should be minimalised. It is recommended to take care of the nail plaque and to use thick, alcohol-free emollients without any skin-drying ingredient.

In case of grade 1 CTCAE side effects, further observation or the topical use of hydrocortisone balm or gel, or balm with clindamycin, is recommended. In the event of a moderate rash (grade 2 CTCAE), an oral antibiotic from the tetracycline group (doxycycline or minocycline) 100 mg twice daily should be added to the aforementioned local treatment. The TKI EGFR therapy should remain unchanged for all patients treated for grade 1 or 2 skin toxicity.

The re-evaluation of the skin changes is recommended in two weeks. If there is no significant improvement or further worsening of the side effects, it is recommended to implement the algorithm for higher grade toxicity. Severe skin toxicity grade 3 or 4 requires a temporal interruption of the TKI EGFR. Regardless of the local treatment, the addition of oral doxycycline and methylprednisolone is recommended. The evaluation of the treatment efficacy should be reassessed in two weeks. Once the symptoms regress to grade 1, the TKI EGFR therapy may be implemented. If there is a renewed episode of grade 3 toxicity despite the appropriate management, the continuation of the TKI EGFR therapy at the reduce dose may be considered. On account of the long half-life of TKI EGFR agents, the treatment of the side effects should be continued until regression of the symptoms to a level accepted by the patient or until its complete resolution.

Currently, the prophylactic use of antibiotics is not recommended. Based on the data from the randomised clinical trials and its meta-analysis, it was proven that prophylactic antibiotic therapy does not reduce the incidence of skin complications. However, the administration of an antibiotic from the tetracycline group reduces the relative risk and prolongs the time to grade 3 and 4 toxicity onset [9].

Diarrhoea

Pathogenesis

The second most common side effect observed during TKI EGFR therapy is diarrhoea. Excess chloride secretion into the intestine lumen or impairment of the intestinal crypts are possible causes of the diarrhoea accompanying TKI EGFR administration. As a consequence, it may lead to electrolyte losses, acid-base imbalance, dehydration, and in extreme cases to renal insufficiency. The diarrhoea associated with a molecularly targeted therapy appears mostly in the first two weeks of treatment.

Table 3. CTCAE diarrhoea grading [8]

Grade	Symptoms
1	Increase of fewer than 4 stools per day
2	Increase of 4–6 stools per day over baseline
3	Increase of 7 or more stools per day over baseline; incontinence; hospitalisation indicated; limits self-care activities of daily living
4	Life-threatening consequences Urgent intervention indicated
5	Death

CTCAE — Common Toxicity Criteria for Adverse Events

Incidence

During TKI EGFR treatment diarrhoea appears in 20% to over 90% of patients. The majority of patients reports CTCAE grade 1 or 2 diarrhoea intensity (Table 3) [6]. Regardless of the CTCAE grade 3 and 4 diarrhoea observed in 15% of patients, the long duration of this side effect in the lower grade may also lead to electrolyte and hydration imbalance or affect the patient's activity and his/her quality of life. In the published results of phase III clinical trials which compared head to head different TKI EGFR, the higher incidence of diarrhoea of any grade (in about 70% of patients) and of grade 3 or higher (in about 10% of patients) was reported in the group treated with the second-generation irreversible TKI EGFR (dacomitinib, afatinib) compared to the group receiving reversible TKI EGFR (erlotinib, gefitinib) in which the diarrhoea of any grade was observed in 33–47% and in grade 3 or higher in about 2% of patients [10, 11]. The appropriate treatment reduces the risk of developing diarrhoea of significant intensity. In the group treated with the irreversible TKI EGFR, diarrhoea led to the discontinuation of the therapy in 3% of patients [12].

Management

Before starting treatment, the first step is to rule out other potential causes of diarrhoea (previous abdomen radiotherapy, laxatives, side effects of antibiotics, excess consumption of fibre dietary factors, and concomitant diseases). The recommended laboratory examinations include the evaluation of renal function, blood presence of electrolyte abnormalities, complete blood count, and a stool culture to detect *Clostridium difficile* or other bacterial pathogenies.

All patients presenting symptoms of diarrhoea should be advised to increase the daily fluid intake and to modify the alimentary habits that may potentially exacerbate the symptoms. Patients should avoid fried, greasy, high-fibre, or spicy food. It is recommended to have 5–6 small meals daily instead of 2–3 bigger ones. It is advised to compensate the fluid loss by drinking a glass of water after each loose stool and 8–10 glasses of fluids during the whole day.

In cases of CTCAE grade 1 and 2 diarrhoea, in addition to the dietary changes it is recommended to administer immediately loperamide at the initial dose of 4 mg, then 2 mg every four hours or every two hours if the diarrhoea persists for more than one day (Table 4). The administration of loperamide should be discontinued after 12 hours have passed with no episodes of diarrhoea. It is crucial to inform the patient treated with TKI EGFR in the outpatient unit about how to use loperamide and what the dietary recommendations are in the event of diarrhoea. If, despite the appropriate management, the symptoms do not improve or exacerbate, we should follow the algorithm for higher grade toxicity.

In patients with symptoms of grade 3 or 4 diarrhoea, in order to prevent dehydration, hospitalisation and a parenteral fluid supplementation are indicated. Beyond the aforementioned symptomatic treatment and the administration of loperamide, it is recommended to temporally withdraw the TKI EGFR therapy until the symptoms regress to grade 1 or completely subside, and then to continue the TKI EGFR treatment at the current or reduced dose. There is no evidence supporting the efficacy of octreotide in severe diarrhoea accompanying TKI EGFR therapy. If the severe diarrhoea recurs, the continuation of the treatment may require a further reduction of the drug dose or TKI EGFR therapy interruption.

Table 4. Managing the diarrhoea

CTCAE Grade	Managing
1 or 2	Adjust diet Loperamide at the beginning 4 mg orally, then 2 mg every 2–4 hours after 12 hours without diarrhoea Continue TKI therapy
3 or 4	See grade 2 recommendations Hospitalisation and parenteral hydration is recommended TKI therapy should be interrupted until regression of the side effects to grade 1

CTCAE — Common Toxicity Criteria for Adverse Events

Hepatotoxicity

Pathogenesis

A less frequent side effect of the TKI EGFR treatment is reversible liver impairment. The hepatotoxicity accompanying the therapy manifests mostly as abnormal laboratory test results (mild or moderate increase of the alanine and asparagine aminotransferase activity and of the bilirubin level), which mostly have a transitional character and do not require discontinuation of the treatment. There are only a few reports of sever liver insufficiency. Among the hepatotoxicity risk factors, we can mention long treatment duration, pre-existing liver pathology, and concomitant use of other potentially hepatotoxic drugs [13].

Incidence

The incidence of liver toxicity during the TKI EGFR therapy probably depends on the *EGFR* mutation status and race. The TKI EGFR related hepatotoxicity of any grade occurs in fewer than 10% of patients in the molecularly unmatched population [13]. In several phase III clinical trials elevated aminotransferases activity was reported in 20–30% of patients with unknown EGFR mutation status, while in patients with identified EGFR mutation the incidence of abnormal aminotransferases levels was estimated at 50% on gefitinib and about 30% on erlotinib. Grade 3 and higher CTCAE toxicity (Table 5) was observed after the administration of gefitinib and erlotinib, respectively, in 18% and 5.4% of patients. Patients of Asian descent are at higher risk of developing this complication [13, 14]. The result of studies exploring the difference of the hepatotoxicity incidence for each TKI EGFR agent are inconclusive, and the observed variation probably results from the changeable enzymatic activity of the liver in each population [15].

We should be aware of the possibility of negative drug interactions — the use of strong CYP3A4 may lead to exacerbation of TKI EGFR toxicity.

Table 5. CTCAE hepatotoxicity grading [8]

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
ALT ↑	> UNL — 3.0 × UNL	> 3.0–5.0 × UNL	> 5.0–20.0 × UNL	> 20.0 × UNL
AST ↑	> UNL — 3.0 × UNL	> 3.0–5.0 × UNL	> 5.0–20.0 × UNL	> 20.0 × UNL
Bilirubin ↑	> UNL — 1.5 × UNL	> 1.5–3.0 × UNL	> 3.0–10.0 × UNL	> 10.0 × UNL

ALT — alanine transaminase; AST — aspartate transaminase; CTCAE — Common Terminology Criteria for Adverse Events

Management

A pre-existing dysfunction of the liver increases the risk of TKI EGFR-induced hepatotoxicity. It is not recommended to start the therapy in persons with severe liver function disorders. The liver function should be controlled during the TKI EGFR treatment (the evaluation of the aminotransferase and bilirubin levels). The majority of cases of liver dysfunctions are asymptomatic and do not require managing. If the level of aminotransferases reaches CTCAE grade 3, after ruling out all other causes of liver dysfunction, it is effective to temporarily discontinue. The treatment may be re-started once the toxicity decreases to grade 1 or completely resolves. A reoccurring grade 3 or higher hepatotoxicity is an indication for dose modification according to the drug characteristic.

Interstitial lung diseases

Pathogenesis

Interstitial lung diseases (ILD) constitute a heterogeneous disease group characterised by disseminated ventilation disorders on the radiologic scans of the chest, with decreased diffusion capacity of the lungs and impaired exchange of respiratory gases. The exact mechanism of ILD induced by TKI EGFR is unknown and is probably due to a decreased protective function of the EGF receptors localised on type 2 pneumocytes.

Incidence

Based on 21 clinical trials including 1468 patients treated with TKI EGFR during the years 2006–2014, the incidence of ILD of at least grade 3 is low and reaches about 2% [13]. No influence of the subsequent treatment lines on the ILD incidence was observed. There was no difference in the incidence of the ILD between Asians and non-Asians (2.5% *vs.* 0.9%, p = 0.11) except for the Japanese population compared to other Asian nationalities (3.8% *vs.* 0.3%, p = 0.0009). Genetic factors and pre-existing lung tissue injuries may promote the development of ILD [16]. The risk factors for ILD associated with TKI-EGFR administration are: previous diagnosis of lung fibrosis, older age, poor performance status, male sex, history of smoking cigarettes, or coexisting heart disease [16]. Despite the low incidence, ILD is the main cause of death related to EGFR TKI therapy.

Management

ILD constitute a heterogeneous group of diseases, which may range from mild radiographic findings of lung infiltrates to life-threatening acute respiratory distress syndrome [17]. There are several histological subtypes of the interstitial lung disease:

— diffuse alveolar injury;
— chronic interstitial pneumonia;
— organising pneumonia;
— eosinophilic pneumonitis;
— granulomatous lung disease [18].

There is a five-grade CTC classification scale of interstitial lung diseases. Grade 1 is characterised only by radiologic changes. In grade 2 and 3 clinical symptoms, with or without limitation of the unassisted functioning are present, and the oxygen therapy is necessary. Grade 4 is a life-threatening condition requiring mechanical ventilation [19]. The symptoms of ILD are uncharacteristic. The most common symptoms are dyspnoea and a dry cough as well as the presence of fine crackles at the lung bases on a physical exam. Routine chest X-ray does not reveal any changes in about 10% of patients. That is why the ILD workup should include a high-resolution computer tomography of the chest (HRCR). A bronchoscopy with the bronco-alveolar lavage (BAL) and a trans-bronchial lung biopsy improve the probability of ILD diagnosis. The symptoms of interstitial lung disease are often analogous to the symptoms of neoplastic disease. That is why any other potential causes of the symptoms must be ruled out before making the diagnosis of TKI EGFR related ILD [20]. The diagnosis of the TKI EGFR-related ILD is based on clinical symptoms, results of the imaging tests (i.a. non-characteristic areas of the ground glass opacities at the lung bases), exclusion of an infection, and progression of the cancer as well as on the clinical improvement after drug withdrawal [21, 22]. The exacerbation of the dyspnoea, cough, or fever of unknown origin observed in the early TKI EGFR treatment phase may be related to the developing ILD.

If ILD is suspected, TKI EGFR treatment should be discontinued during the diagnosis and, once the diagnosis of ILD is confirmed, the TKI EGFR must be stopped regardless of the ILD severity, and administration of steroids should be considered. In view of the low incidence of this complication, there are no prospective clinical trials evaluating the treatment modalities in interstitial lung diseases related to the use of TKI. According to the recommendations it is indicated to implement methylprednisolone at the daily dose of 1 g intravenously over three days and then prednisolone at the dose of 60 mg/day orally with a gradual dose reduction of 10 mg per week.

Summary

Side effects of TKI EGFR are observed in the majority of patients (Table 6); however, unlike the toxicity of chemotherapy they are rarely life threatening.

Table 6. The incidence of the most common TK treatment complications (in brackets — the side effects of grade 3 or higher by CTCAE)

Drug	Erlotinib		Gefitinib		Afatinib	
	Clinical trial, population (any grade/grade 3 and 4) (% of patients)					
Side effects, incidence	EURTAC Caucasian [3]	OPTIMAL Asian [24]	IPASS Asian [2]	WJTOG3405 Asian [25]	LuxLung3 Caucasian and Asian [23]	LuxLung6 Asian [26]
Rash	89/13	73/2	66/3	74/2	89/16	88/5
Diarrhoea	57/5	25/1	47/4	47/1	95/14	81/14
Elevated ALT/AST	80/5	37/4		61/24	ND	20/2
Tiredness	57/6	5/0	ND	34/2	18/1	10/< 1
Nail changes/paronychia	ND	4/0	14/< 1	28/1	56/11	33/0
ILD	1/1	0	3/ND	< 1	1/ND	< 1

ALT — alanine transaminase; AST — aspartate transaminase; CTCAE — Common Terminology Criteria for Adverse Events; ND — no data

In the majority of randomised clinical studies, in less than 8% of patients toxicity led to the discontinuation of treatment [2, 3, 23]. In clinical practice, following the recommendations of the prevention and treatment of the side effects enables the accomplishment of the treatment plan, and in consequence — compared to the chemotherapy — influences the quality of life and the rate of longstanding overall survivals in patients with a predictive marker, treated with TKI EGFR.

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