

Tyrosine Kinase Inhibitors against Cancer: Their Safety in 216 Moroccan Patients

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How to cite this paper: Nouiakh, L., Oualla, K., Ouafki, I., Berrad, S., Erraichi, H., Amaadour, L., Benbrahim, Z., Arifi, S. and Mellas, N. (2021) Tyrosine Kinase Inhibitors against Cancer: Their Safety in 216 Moroccan Patients. *Journal of Cancer Therapy*, 12, 116-126.

<https://doi.org/10.4236/jct.2021.123013>

Received: January 7, 2021

Accepted: March 9, 2021

Published: March 12, 2021

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Abstract

Tyrosine kinase inhibitors (TKIs) have become a prominent option in the therapeutic arsenal of several cancers. The safety of these drugs has shown various toxicities with varying frequency and severity between different agents. The aim of this study is to describe the safety profile of different classes of TKI used in various solid tumors. It is a retrospectively descriptive study conducted in the Department of Medical Oncology at Hassan II University Hospital of Fez, Morocco, over a period of 6 years from April 2013 until April 2019. It included 216 patients who received one or more TKI for different indications in solid tumors. The average age in our series was 61.4 years with a sex ratio F/M of 1.07. Among the most used TKIs in our department according to their availability: Imatinib (32%) and sunitinib (32%). All patients received one or more tyrosine kinase inhibitors according to the indication. Kidney cancer was the most common malignancy (36%), followed by gastrointestinal stromal tumors (33%). The median duration of treatment was 15 months with extremes of 1 month and 102 months. The main side effects were: Cutaneous in 43% of patients. Digestive toxicity occurred in 36% of cases. Hematotoxicity was reported in 33% of cases. The safety profile of TKIs used in our study was comparable to their global tolerance reported in literature. More studies are needed to investigate the relationship between their toxicity and their efficacy in Moroccan population.

Keywords

Tyrosine Kinase Inhibitors, Safety, Side Effects

1. Background

Since 1998, new drug therapies have been discovered. Their mode of action mainly relates to the transduction of cell proliferation signals. Among these

therapies, we find tyrosine kinase inhibitors.

Tyrosine kinase inhibitors (TKIs) represent an important therapeutic class in the management of patients with solid tumors. TKIs are small molecules of the quinazoline family that will diffuse across the cell membrane by targeting the signal transduction process at receptor tyrosine kinase [1]. TKIs are subdivided into several classes depending on the type of TK targeted: TKIs that target the EGFR pathway such as Gefitinib, Erlotinib, Lapatinib and Afatinib, TKIs that target the c-KIT pathway (Imatinib, Sunitinib) and TKIs of the VEGFR pathway (Sorafenib, Sunitinib, Axitinib, Pazopanib, Vandetanib, Regorafenib, Tivozanib, Vatalanib). TKIs bind to the ATP binding sites of receptor tyrosine kinases and block their activation. Consequently, the proliferation of cancer cells is inhibited [2].

These molecules are used especially in advanced or metastatic forms of cancer. Several studies have proven their effectiveness in terms of survival compared to conventional chemotherapy [1]. Most TKIs have a denomination ending with the suffix “IB”. They work by competitively binding to the ATP binding sites of receptor tyrosine kinase. However, despite a specific intracellular mechanism of action, these agents are not immune to the problem of tolerance [3], because, they can be the source of several adverse effects. Tolerance of TKI may be influenced by the existence of comorbidities. There is great inter-individual variability in the occurrence of adverse effects, the mechanisms of which are still poorly understood.

The aim of this study is to describe the main adverse effects induced by TKIs of different classes, used for the treatment of solid tumors in our population and to compare our results with those reported in the literature.

2. Methods

2.1. Type of the Study

This is a descriptive retrospective study carried out in the medical oncology service of the Hassan II University Hospital in Fez, Morocco, over a period of 6 years from April 2013 to April 2019 in 216 patients.

2.2. Study Population

The inclusion criteria were: people over 18 years old, with a solid malignant tumor confirmed by histology, treated with one of the following TKIs: Sunitinib, Pazopanib, Sorafenib, Axitinib, Erlotinib, Afatinib, Imatinib and Regorafenib for different indications in solid tumors.

Epidemiological, clinical and therapeutic data as well as the safety profile were collected from medical files in their computerized form (available in the hosix software) or through files archived in the medical oncology department.

The various pieces of informations were listed in an exploitation sheet, established after bibliographic research and literature review.

Statistical analysis is done by SPSS version 23 software, qualitative variables

are expressed as frequency and percentage and quantitative variables are expressed as median, mean and standard deviation.

3. Results

The mean age in our series was 61.4 years with age extremes ranging from 20 to 95 years. There was a slight female predominance (sex ratio F/M of 1.07). Among the TKIs most used in our service according to their availability: Imatinib (32%), sunitinib (32%), sorafenib (10%), lapatinib (10%), pazopanib (7%), afatinib (5%), erlotinib (2.5%), regorafenib (1%) and axitinib (0.5%). All patients received one or more TKIs depending on the indication. Kidney cancer was the most common cancer (36%) followed by gastrointestinal stromal tumors (33%), breast cancer (10%), non-small cell lung cancer (7.5%), carcinoma thyroid (5.5%), hepato-cellular carcinoma (4%) and other tumors (4%) (**Table 1**). The median duration of treatment was 15 months with extremes of 1 and 102 months. The main side effects were: cutaneous observed in 43% of patients; dominated by skin rash (under anti-EGFR: 50% (grade 3 and 4: 22.5%)) (**Figure 1**), then hand-foot syndrome (on anti-VEGFR: 59.5% (grade 3 and 4: 7%)) then

Table 1. Patient characteristics.

Characteristics	Number (%)	
Gender	Male	100 (46)
	Female	116 (54)
Age	<40 years	24 (11)
	Between 40 and 60 years	76 (35)
	Between 60 and 80 years	108 (50)
	>80 years	8 (4%)
TKI studied	Imatinib	69 (32)
	Sunitinib	69 (32)
	Sorafenib	22 (10)
	Lapatinib	22 (10)
	Pazopanib	15 (7)
	Afatinib	11 (5)
	Erlotinib	5 (2.5)
	Regorafenib	2 (1)
TKI indications	Axitinib	1 (0.5)
	Kidney cancer	78 (36)
	GIST	71 (33)
	Breast cancer	22 (10)
	Lung cancer	16 (7.5)
	thyroidcarcinoma	12 (5.5)
	HCC	9 (4.5)
Others	8 (4)	

hair damage (alopecia: 65% on anti-VEGFR, hair depigmentation: 7% under suinitinib) (**Figure 2** and **Figure 3**), and lastly, nail damage such as paronychia (anti-EGFR: 52.5%) and sub-nail haemorrhages (anti-VEGFR: 43.7%) (**Figure 4**). Digestive toxicity occurred in 36% of cases, it was in the form of diarrhea (on anti-EGFR: 62.5% (grade 3 and 4: 14.5%)), nausea-vomiting (on anti-VEGFR: 34% (grade 3 and 4: 5.5%)) and stomatitis (anti-EGFR: 55%, anti-VEGFR: 37.5% (grade 3 and 4: 2%)). Hematotoxicity was reported in 33% of cases; anemia (anti-EGFR: 30%) and thrombocytopenia (anti-EGFR: 20%). Pulmonary toxicity occurred in only one patient who experienced hemoptysis on sorafenib. Asthenia was observed with all three classes of ITK studied. Under antiangiogenic treatment; 10% hypothyroidism, 7.3% high blood pressure, and 1.3% proteinuria were noted, and no cases of thromboembolic complications were reported. No “fatal” adverse events were observed in our patients.

Table 2 summarizes the various adverse effects induced by TKIs in our study.



Figure 1. Skin rash under anti-EGFR (medical oncology service of CHU Hassan II in Fez, Morocco).



Figure 2. Hand-foot syndrome under anti-VEGFR (medical oncology service of CHU Hassan II in Fez, Morocco).



Figure 3. Hair depigmentation under sunitinib (medical oncology department of CHU Hassan II in Fez, Morocco).



Figure 4. Paronychia under anti-EGFR (medical oncology department of CHU Hassan II in Fez, Morocco).

4. Discussion

The most common side effects with TKIs are: Skin involvement dominated by skin rash which represents the most frequent side effect, it is common to all targeted therapies studied with a different clinical presentation depending on the class of TKI received [4]. There are three types of rash: Acneiform rash, observed with anti-EGFR TKIs [5]; it is an acne-like rash, found in 45% to 100% of cases depending on the studies [6] [7]. In our series, it was observed in 50% of cases. It appears within eight to ten days of treatment starting, mainly affecting the face and upper trunk [4] [8]. The intensity of the skin rash correlates with the therapeutic response to anti-EGFR; the more severe the skin reaction, the better the response [6] [7] [8] [9], this can be explained by the better bioavailability of the product and the beneficial effect of the immune reaction in the tumor and also in the skin [9]. The second type of rash is seborrheic dermatitis, it concerns anti-VEGFR drugs, manifests itself clinically in the form of an erythema with

Table 2. Main adverse effects induced by TKIs in our series.

Sideeffects	TKI class/molecule	Percentage (%)
Skin involvement Rash	Anti-EGFR	27.5 (G1, G2), 22.5 (G3, G4)
	Anti-VEGFR	29.5 (G1, G2)
	c-Kitinhibitors(imatinib)	11 (G1, G2)
Hand-foot syndrome	Anti-EGFR	17.5 (G1, G2)
	Anti-VEGFR	52.5 (G1, G2), 7 (G3, G4)
	c-Kitinhibitors(imatinib)	0
Xerosis	Anti-EGFR	35 (G1, G2)
	Anti-VEGFR	25 (G1, G2)
	c-Kitinhibitors(imatinib)	17 (G1, G2)
Yellowish discoloration of the skin	Sunitinib	14
Skin depigmentation	Imatinib	12.5
Hair damage Alopecia	Anti-EGFR	37.5
	Anti-VEGFR	65
	c-Kitinhibitors(imatinib)	35
Texture modification	Anti-EGFR	45
	Anti-VEGFR	82
	c-Kitinhibitors(imatinib)	0
Depigmentation	Sunitinib	7
Nailinvolvement Paronychia	Anti-EGFR	52.5
	Anti-VEGFR	43.7
Digestive damage Diarrhea	Anti-EGFR	47.5 (G1, G2), 15 (G3)
	Anti-VEGFR	32 (G1, G2), 4.5 (G3)
	c-Kitinhibitors(imatinib)	22
Nausea/vomiting	Anti-EGFR	37.5 (G1, G2)
	Anti-VEGFR	28.5 (G1, G2), 5.5 (G3)
	c-Kitinhibitors(imatinib)	34.7 (G1, G2)
Stomatitis	Anti-EGFR	55 (G1, G2)
	Anti-VEGFR	37.5 (G1, G2), 2 (G3, G4)
	c-Kitinhibitors(imatinib)	1.5 (G1, G2)
Hematologicinvolvement Anemia	Anti-EGFR	30 (G1, G2)
	Anti-VEGFR	35 (G1, G2), 1.8 (G3, G4)
	c-Kitinhibitors(imatinib)	24 (G1, G2), 2.7 (G3, G4)
Thrombocytopenia	Anti-EGFR	20 (G1, G2)
	Anti-VEGFR	18 (G1, G2), 4.5 (G3, G4)
	c-Kitinhibitors(imatinib)	12.5 (G1, G2)

Continued

	Anti-EGFR	0
Neutropenia	Anti-VEGFR	3 (G1, G2), 0.9 (G3, G4)
	c-Kitinhibitors(imatinib)	2.8 (G1, G2)
	Anti-EGFR	30 (G1, G2)
<i>Asthenia</i>	Anti-VEGFR	41 (G1, G2), 18.7 (G3, G4)
	c-Kitinhibitors(imatinib)	39 (G1, G2)
	<i>Others:</i>	
Edemas	Imatinib	35
Hypothyroidism	Anti-VEGFR	10
Arterial hypertension	Anti-VEGFR	7.3
Proteinuria	Anti-VEGFR	1.3
Thrombosis	Anti-VEGFR	0

Legende: TKI: tyrosine kinase inhibitors, G1: grade 1, G2: grade 2, G3: grade 3, G4: grade 4.

desquamation, the topography of the lesions varies depending on the molecule administered, it occurs in the first weeks of treatment [10] [11]. The last type of rash is allergic rash, observed with c-Kit inhibitors such as imatinib, the clinical presentation is manifested in the form of itchy papules and macules involving the face, trunk, forearm and the legs [12] [13], as is the case in our study.

Another type of skin involvement can be seen with TKIs; it is the hand-foot syndrome: it is found especially with anti-angiogenic treatments, but it can be observed with anti-EGFR more particularly with lapatinib, but only within the framework of a combination of lapatinib and capecitabine [14]. Under anti-angiogenic treatment, this syndrome results in hyperkeratosis in the areas of friction, the evolution can be marked by the appearance of a bullous detachment or become inflammatory [10]. In the hand-foot syndrome seen with lapatinib, the clinical symptomatology is redness with edema [14]. Sometimes they can appear dander, ulcerations and bleeding. In our study, this syndrome was observed in 59.5% under antiangiogenic therapy and in 17.5% under lapatinib.

Xerosis is another type of skin toxicity; observed with all TKIs. In our study, it was noted in 35% of cases under anti-EGFR treatment, 25% under anti-angiogenic drugs and in 17% under Imatinib. Our results were similar to those reported in the literature, xerosis affects one third of patients on anti-EGFR and anti-VEGFR after two to three months of treatment [9] [15], and it is clinically manifested by itching dryness, even painful with weakened skin [9] [16]. The yellowish discoloration of the skin is a toxicity associated with treatment with sunitinib. In our series, it was observed in around 14% of patients treated with sunitinib, this percentage can go up to 30% depending on the studies [10]. This coloration indicates an impregnation of the product but its presence and its intensity are not correlated with the effectiveness of the drug. Arriving at phantheric attacks; hair damage can be clinically manifested in three ways depending on the

treatment received: alopecia, changes in texture and depigmentation of the hair. Beginning with alopecia, it has been found in the different classes of ITK studied with predominance in patients receiving anti-VEGFR. In the literature, it has been reported with anti-EGFR, anti-VEGFR and c-Kit inhibitors (imatinib) with a time to onset and a topography varying according to the treatment received [9]. On anti-EGFR, alopecia may develop two to three months after treatment starting. It concerns the vertex and the temporal gulfs mimicking androgenic alopecia [9]. On anti-VEGFR, alopecia is temporary with hair regrowth while continuing treatment [9] [10]. There are no data regarding the time to onset and the topography of it. Regarding changes in hair texture, they are seen mainly with anti-EGFR and anti-VEGFR treatments [15]. In our study, they were found in 82% and 45% of cases under anti-VEGFR and anti-EGFR respectively, the hair becomes fragile and dry. Hair depigmentation is a specific sign of sunitinib, which appears more or less late (four to six weeks after the initiation of treatment), it is characterized by alternating depigmentation and repigmentation of the hair, a “flag sign” [10] [17]; noted in 7% of patients who received sunitinib in our study. About nail abnormalities; there are two types of attacks: Paronychia and subungual hemorrhages. Paronychia is found especially with anti-EGFR, they appear one to three months after the start of treatment [9], they are manifested by edema with erythema, sometimes they can appear as fleshy buds on the edges of the nails [4] [15]. In our series, they were present in 52.5% of cases under anti-EGFR. The second type of nail involvement is subungual hemorrhage; observed with anti-VEGFR in 43.7% in our study. They appear after the first four weeks of treatment as dark red or black longitudinal bands in the distal part of the nails [17].

Another type of toxicity associated with treatment with TKIs is gastrointestinal toxicity; found in 36% of cases in our series, it was in the form of stomatitis, diarrhea and nausea-vomiting. Beginning with diarrhea; this is an adverse reaction observed with all the targeted therapies studied in our series, were common in patients receiving anti-EGFR with a percentage of 62.5%. According to the data in the literature, diarrhea appears in the first weeks after treatment and can be explained by a direct toxic effect of therapies targeted on the intestinal mucosa [18]. Stomatitis is observed mainly with anti-VEGFR and anti-EGFR, the clinical presentation is identical to the two therapeutic classes, they appear during the first two months [11]. In our series, they were noted in 55% and 39.5% under anti-EGFR and anti-VEGFR respectively. With regard to nausea and vomiting; generally, targeted therapies are weakly emetic [19], this emetizing potential may increase in the presence of risk factors (age less than 50 years, female sex, presence of anxiety, poor vomiting control during previous chemotherapy) [19]. Other side effects can be seen with TKIs, such as bone marrow suppression; it is observed especially with antiangiogenics and with c-Kit inhibitors, it is generally of low to moderate grade, rarely of severe grade [11] [20]. It occurs in the first months of treatment with imatinib [20], and in the third, fourth week of

treatment with antiangiogenics [11]. Edema has been observed with imatinib; noted in 35% of patients receiving imatinib in our series. They most often occur in the lower limbs and periorbital. According to the literature, this percentage can go up to 60% [21] [20]. Arterial hypertension is a frequent sign under anti-VEGFR treatment, found in 5.3% in our series, this rate remains relatively low compared to that reported in the literature, this can be explained by the decline in treatment which was not enough important in our series because hypertension is a sign of late and slow onset [22] [23]. Its occurrence could be favored by the presence of the following factors (hypertension before initiation of treatment, presence of coronary artery disease, presence of renal cancer [24]). Hypothyroidism is a specific side effect of anti-angiogenic treatments; especially sunitinib [22], the correlation between hypothyroidism and treatment efficacy has been demonstrated in animal models, yet to be proven in humans.

5. Conclusion

Overall, the safety profile of the TKIs used in our study was comparable to that reported in the literature. Further studies are needed to study the relationship between their toxicity and their efficacy in the Moroccan population.

Funding

The authors received no specific funding for this study.

Conflicts of Interest

The authors declare that they have no competing interests.

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