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Short Communication

Hypertensive toxicity of thyrosine kinase inhibitors; Friend or Foe?

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Abstract

Tyrosine kinase inhibitors (TKIs) are widely used in Oncology practice. Hypertension may develop during cancer treatment and TKIs are well known drugs that are associated with drug related hypertensive toxicity. TKI related hypertensive toxicity is not always the indicator of worse clinical outcomes and it may be the sign of treatment efficacy.

More Information

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The development of new targeted therapies such as tyrosine kinase inhibitors (TKIs) has led to dramatic survival benefit in cancer patients. TKIs affects several pathways including cell proliferation and angiogenesis. Angiogenesis plays crucial role in tumor growth and metastasis, therefore inhibition of angiogenesis is one of the main goals in cancer treatment [1]. Vascular endothelial growth factor (VEGF) is the main mediator of angiogenesis and tyrosine kinase inhibitors (TKIs) which are used in several malignancies including; renal cell carcinoma, hepatocellular carcinoma, medullar thyroid carcinoma, colorectal carcinoma and gastrointestinal stromal tumor have VEGF signaling pathway inhibitory effects [2]. There are three subtypes of VEGF receptors and VEGF exerts its thyrosine kinase pathway related effects via VEGF receptor 2 (VEGFR2). VEGF causes nitric oxide (NO) production, endothelial cell proliferation and migration, increased vascular permeability and survival under stress conditions. VEGF inhibition leads to decreased levels of vasodilatory mediators including NO and prostacyclin and is also associated with decreased survival of endothelial cells resulting in increased peripheral vascular resistance [3].

Cancer treatment related hypertensive cardio toxicity is graded into 5 classes according to the Common Terminology Criteria for Adverse Events (CTCAE) report. Approach to the patients with different grades of hypertensive cardio toxicity is presented in table 1. Several anti-cancer drugs other than VEGF inhibitors also may cause hypertensive cardio toxicity [4].

TKI related hypertension usually develops in the first week of the treatment and it is dose dependent in general. Patients who are candidates for TKI treatment should be evaluated before the treatment and blood pressure should be controlled

Table 1: CTCAE Grades of Hypertensive Toxicity and Management.

CTCAE Grade	Definition	Management
Grade 1	-SBP: 120-139 mmHg -DBP: 80-89 mmHg	Lifestyle modification
Grade 2	-SBP: 140-159 mmHg -DBP: 90-99 mmHg -Increase of 20 mmHg in DBP with symptoms	Drug monotherapy
Grade 3	-SBP > 160 mmHg -DBP >100 mmHg	Drug combination
Grade 4	Malignant hypertension (Retinopathy with BP > 200/120 mmHg) Hypertensive crisis	Urgent parenteral treatment
Grade 5	Death	--

Abbreviations: SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure

1 week before the TKI administration. Blood pressure should be monitorised during the first cycle of the treatment and it should be checked in every 2-3 weeks until the end of treatment. Target values for blood pressure are < 140 mmHg for systolic pressure and < 90 mmHg for diastolic pressure. Even it is in the target range; increase in diastolic blood pressure more than 20 mmHg should direct the clinicians to start antihypertensive treatment [5].

Proteinuria may develop as a consequence of uncontrolled chronic hypertension and some glomerulonephritis may present with proteinuria and hypertension. In addition, some of the glomerular diseases may occur as paraneoplastic syndrome. It is expressed that VEGF inhibition causes reduction in nephrin production which ends in interruption of the glomerular fenestrated endothelium [6]. Therefore it

should be kept in mind that thyrosine kinase inhibitors may cause both hypertension and proteinuria.

Although the development of hypertension is result of VEGF inhibitor toxicity; it may also be a sign of treatment efficacy of the anticancer drug. It is shown in SELECT trial that; development of up to Grade 3 hypertensive toxicity during Lenvatinib treatment was associated with better outcomes in patients with metastatic differentiated thyroid carcinoma [7]. Lenvtatinib which is used in advanced stage differentiated thyroid carcinoma and hepatocellular carcinoma is a multikinase inhibitor and it inhibits not only VEGF receptors but also RET and KIT receptors. Therefore; the incidence of hypertensive toxicity is more frequent in patients treated with Lenvatinib than other TKIs [8].

It is reported in a meta-analysis that occurrence after treatment with Sorafenib was related to longer progression free survival and overall survival in different cancer types [9]. Similar prognostically beneficial effects have been observed in Axitinib [10].

Treatment of hypertension in cancer patient is an important goal in order to be able to administer higher effective doses of TKIs and provide patients from hypertension related complications. Choice of antihypertensive drug should be based upon coexisting comorbidities. It should be kept in mind that diltiazem may reduce the effects of anticancer drugs due to drug interactions via CYP450 enzymes. TKIs may cause prolongation of corrected QT; therefore diuretics should not be preferred as frontier lines in treatment due to their possible adverse effects on electroloyte levels. ACE inhibitors and dihydropyridine calcium channel blockers may be the safe option in cases with TKI related hypertension [3].

Conclusion

Although hypertensive toxicity is an undesirable result of TKI use; it may be the sign of the treatment efficacy and better disease outcomes in cancer patients. If TKI related hypertensive toxicity develop in a patient; TKIs should be discontinued temporarily, antihypertensive treatment should be started and TKI should be read ministered after blood pressure control.

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