Laryngeal Side Effects of Tyrosine Kinase Inhibitors

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Summary: Objectives. Tyrosine kinase inhibitors (TKIs) are common targeted drugs, used in the treatment of hematological and solid malignancies. These drugs present a multitude of potential adverse effects. Laryngeal manifestations, including laryngeal edema, secondary to TKIs treatment have not been well studied, despite their potential lethality.

Methods. This cross-sectional study included adult patients (>18 years) treated with TKIs who were followed in a secondary medical center and underwent a voluntary otolaryngological examination, which included laryngeal fiber-optic laryngoscopy (FOL). FOL was independently performed by two senior otolaryngologists, and results were recorded and evaluated by two grading systems, to assess the degree of laryngeal edema. In addition, medical files were reviewed, and data collected included past medical history, signs and symptoms, physical examination, laboratory results, treatment type, and duration.

Results. Sixteen patients, aged 68.2 ± 13.6 years, were examined during October 2014 to December 2014. Of them, three (19%) were males. Eleven (68%) patients presented with varying degrees of laryngeal edema. A significant correlation was found between gastroesophageal reflux symptoms and laryngeal edema ($P = 0.02$). TKI treatment was stopped in one patient, because of symptomatic laryngeal edema, which completely resolved within 2 weeks.

Conclusions. Laryngeal edema was common in our study group. This edema was most often not life threatening. Yet, because of the potential severity of this side effect, we propose a routine FOL examination of patients before commencing TKI treatment and a reevaluation performed during treatment.

Key Words: Tyrosine kinase inhibitor–Larynx–Edema–Fiber-optic laryngoscopy.

INTRODUCTION

Tyrosine kinase inhibitors (TKIs), commonly referred to as "tyrphostins," are antineoplastic drugs which block the activation of many proteins by signal transduction cascades. Their mechanism of action is inhibition of the transfer of phosphate from adenosine triphosphate to tyrosine residues in the catalytic domain of growth factor receptors. Their targets are involved in the survival, proliferation, invasiveness and angiogenesis of tumors, and the induction of apoptosis in cancer cells.[1,2] TKIs are usually better tolerated than most conventional chemotherapies. Over the past 2 decades, TKIs revolutionized the treatment of chronic myeloid leukemia (CML).[1,2] There has also been an increase use of TKIs in the treatment of patients with various solid and other hematological malignancies.[1,2] The potential multitude of side effects produced by TKIs activity is related to various factors: the specific drug used, duration of treatment, administered dose, age and sex of the patient.[3,4] The reported side effects in the head and neck region include facial edema (including palpebral edema), shortness of breath, cough, swallowing difficulties, oral lesions, sialorrhea/xerostomia, epistaxis, nasopharyngitis, gastroesophageal reflux disease (GERD), thyroid function abnormalities, and hoarseness. The frequency of these side effects varies from very rare (~1%) to relatively common (~33%).[5] Most of these side effects are not life threatening, although some may be quite bothersome.

Nonspecific airway symptoms, such as inspiratory stridor, hoarseness, tachypnea, or dyspnea, have been described in patients treated with TKIs, and were attributed to pulmonary and gastroesophageal sequelae. However, these symptoms may potentially be secondary to laryngeal edema, which may be life threatening and which should be excluded. An office-based, physical examination cannot diagnose laryngeal edema. Yet, an examination using a fiber-optic laryngoscopy (FOL) can diagnose edema, estimating its extent and severity. To date, this examination is not used on a routine basis in patients before or during TKI treatment.

This study was conducted to assess the prevalence of laryngeal TKI's side effects, and in particular laryngeal edema, as well as to assess the utility of FOL in the evaluation of these patients before and during treatment.

METHODS

Study design and population

The study was approved by the Edith Wolfson Medical Center institutional review board. We prospectively identified patients (>18 years) who were treated with TKIs and were followed in the Hematology/Oncology clinics in our secondary medical center facility between October 2014 and December 2014. There were 25 eligible patients during the study period; of them, four died during this period, and five others were treated with multiple medications (including other chemotherapy agents), which precluded them from participation in the present study. Recruitment of patients was done by the treating hematologist/oncologist; thus, there was no bias of selection in favor of patients who had laryngeal symptoms. Eligible patients were

Accepted for publication July 14, 2015.
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Journal of Voice, Vol. 30, No. 5, pp. 606-610
0892-1997/$36.00

http://dx.doi.org/10.1016/j.jvoice.2015.07.006

TABLE 1.
Demographic Data

Patient	Gender (F, Female; M, Male)	Age (y)	Tumor Type	Treatment	Dose (mg)	Duration (d)	Medical History	Smoking	Thyroid Function (N = normal)	Facial Edema	GERD*
1	F	64	GIST†	Imatinib	400	30	CVD‡ RD§ S/P parathyroidectomy	+	N	+	+
2	F	65	GIST	Imatinib	400	720	CVD Hypothyroidism	+	N	+	N
3	F	89	NSCLC‖	Erlotinib	150	7	CVD	–	N	+	N
4	F	75	NSCLC	Erlotinib	150	30	CVD	–	N	N	N
5	F	85	CML¶	Imatinib	400	360	CVD	–	N	+	N
6	F	62	CML	Imatinib	400	1080	CVD	–	N	N	N
7	M	68	CML	Imatinib	400	150	CVD	–	N	+	N
8	F	79	CML	Nilotinib	200	360	CVD Hypothyroidism	–	N	N	N
9	F	70	CML	Nilotinib	200	1080	-	+	N	N	N
10	F	52	CML	Nilotinib	200	480	-	–	N	+	+
11	M	64	CML	Imatinib	400	1440	-	–	N	N	+
12	F	77	CML	Imatinib	400	4320	Hypothyroidism	–	N	+	+
13	F	72	HCC#	Sunitinib	37.5	60	CVD	–	N	N	+
14	M	82	CML	Imatinib	400	3960	CVD	–	N	+	+
15	F	49	CML	Nilotinib	400	210	Hypothyroidism	–	N	N	N
16	F	38	CML	Dasatinib**	100	360	-	–	N	N	N

* Gastroesophageal reflux.
† Gastrointestinal stromal tumor.
‡ Cardiovascular disease.
§ Respiratory disease.
‖ Non–small-cell lung cancer.
¶ Chronic myeloid leukemia.
# Hepatocellular carcinoma.
** Previously treated with imatinib for 3 years.