[Translated article] Ruxolitinib and Squamous Cell Carcinoma

Ruxolitinib y carcinoma de células escamosas

To the Editor,

Ruxolitinib is a JAK1 and JAK2 inhibitor approved in 2011 to treat myelofibrosis (MF), polycythemia vera (PV) (in 2014), and graft-versus-host disease (GVHD) (in 2019). Since the initial clinical trials with ruxolitinib, a possible increase in the incidence of non-melanoma skin cancer (NMSC) has been observed. Of note that this drug is used in patients who have a higher risk in relation to the overall population of developing NMSC due to their hematological neoplasms and previous treatments (e.g., hydroxyurea). In addition to this increased incidence, cases of exceptionally aggressive squamous cell carcinoma (SCC) have been reported in patients on ruxolitinib.

We describe the cases of 3 men who developed high-risk SCC while on ruxolitinib administered for hematological conditions. Table 1 shows the patients’ clinical and demographic characteristics. Patient #1 and patient #3 died due to the progression of their skin neoplasms, initially located in both patients in the pinna (figs. 1 and 2). Although patient #2 died shortly after the initial intervention of an unrelated medical problem, the presence of poor prognostic tumor factors, such as perineural invasion or nasal cartilage infiltration, is significant (fig. 2). Ruxolitinib is one of the most widely used drugs to treat patients with myeloproliferative syndromes and corticosteroid-refractory GVHD as it is one of the very few treatments that has proven capable of improving overall survival (in both MF and PV) and disease-free survival (in GVHD). The 5-year assessment of the COMFORT-II clinical trial—which ultimately led to the approval of the indication for MF treatment—confirmed a 17.1% incidence rate of NMSC (25 out of 146) in patients on ruxolitinib vs a 2.7% incidence rate (2 out of 73) in the control group on the optimal medical therapy. However, after adjusting for exposure (patient-years), this difference did not reach statistical significance.

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Table 1  Main characteristics of patients who developed high-risk SCC while on ruxolitinib.

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<tr>
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<th>Patient #1</th>
<th>Patient #2</th>
<th>Patient #3</th>
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<tbody>
<tr>
<td>Age and sex</td>
<td>77 years. M</td>
<td>85 years. M</td>
<td>69 years. M</td>
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<tr>
<td>Hematological history</td>
<td>JAK2 positive MF</td>
<td>JAK2 positive PV</td>
<td>Bone marrow transplant for mantle cell lymphoma, non-Hodgkin type GVHD</td>
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<td>Ruxolitinib (dose; prior exposure time)</td>
<td>10 mg/12 h; 19 months</td>
<td>10 mg/12 h; 26 months</td>
<td>10 mg/12 h; 2 months</td>
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<td>Clinical presentation</td>
<td>Infiltrating tumor (3.5 cm in diameter) located in the upper and middle thirds of the right pinna (fig. 1A and 1B)</td>
<td>Rapidly growing crusty tumor (15 mm in diameter) located on the right nasal wall (fig. 2A)</td>
<td>Rapidly appearing and bleeding lesion on the right pinna over a previous GVHD angiomatous location (fig. 2E and 2F)</td>
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<td>Treatments</td>
<td>Complete amputation of the pinna, right superficial parotidectomy, and right functional neck dissection (fig. 1C) + RT to surgical bed and lymph node chains (62.5 Gy and 49.5 Gy, respectively)</td>
<td>Lesion excision, during surgery massive macroscopic deep infiltration was seen (fig. 2B and 2C), so total skin graft coverage was decided, with subsequent evaluation for RT SCC contacting deep margin and perineural infiltration of a 0.13 mm nerve (fig. 2D)</td>
<td>Initially treated with RT at 16 Gy. Due to persistent lesion, surgical amputation and ipsilateral functional neck dissection were decided.</td>
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<td>Histological study</td>
<td>Moderately differentiated SCC (fig. 1D), 15 mm deep infiltration, and presence of lymphovascular invasion. Surgical margins, 8 cervical nodes removed, and tumor infiltration-free parotid</td>
<td>Moderately differentiated SCC, with clear margins and lymph nodes without metastatic involvement</td>
<td>Moderately differentiated SCC, with clear margins and lymph nodes without metastatic involvement</td>
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<td>Outcome</td>
<td>12 months later, appearance of bilateral cervicothoracic lymphadenopathy and metastatic pleural effusion (fig. 1E and 1F). Deceased</td>
<td>Further studies or treatments were not possible after the patient’s death from another unrelated medical issue</td>
<td>1 month after surgery, the patient developed metastasis a few centimeters from the operated region and treatment with cetuximab was initiated, passing away after 2 sessions of treatment</td>
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GVHD, graft-versus-host disease; M, male; MF, myelofibrosis; PV, polycythemia vera; RT, radiotherapy; SCC, squamous cell carcinoma.
Figure 1  Images from patient #1. A and B) Clinical appearance of SCC affecting the upper and middle thirds of the right pinna. C) Functional neck dissection. The image shows the external jugular vein, the parotid gland, and the facial nerve. D) Hematoxylin and eosin stain, 200x. Moderately differentiated keratinizing tumor forming keratin pearls. E) Coronal image, contrast-enhanced computed tomography (CT) showing right supraclavicular lymphadenopathy (circle); asterisk indicates pleural effusion. F) Cross-sectional image, contrast-enhanced CT, asterisk indicates pleural effusion.

Figure 2  A) Patient #2, squamous tumor on the nasal wall. B and C) Intraoperative appearance suggesting deep infiltration of nasal cartilages. D) Hematoxylin and eosin stain, 200x, showing tumor with perineural infiltration. E and F) Patient #3, large fleshy tumor with spontaneous bleeding affecting almost the entire pinna.

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Conflicts of interest
None declared.

References


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