Dose-limiting stomatitis associated with ibrutinib therapy: a case series

Ibrutinib, a Bruton tyrosine kinase (BTK) inhibitor approved by the European Medicines Agency and US Food and Drug Administration, is effective for patients with chronic lymphocytic leukaemia (CLL), relapsed mantle cell lymphoma and Waldenström macroglobulinemia (Byrd et al, 2013, 2014; Burger et al, 2015; Pula et al, 2017; Ransohoff & Kwong, 2017). Commonly reported adverse events include diarrhoea, infection, fatigue, arthralgias, pyrexia, hypertension and neutropenia (Byrd et al, 2013, 2014; Burger et al, 2015; Pula et al, 2017; Tran & O’Brien, 2017). However, the rate of grade ≥3 adverse events remains low and treatment discontinuation due to toxicity (Byrd et al, 2013, 2014) is uncommon and mostly related to infections (Byrd et al, 2013, 2014; Burger et al, 2015; Pula et al, 2017; Tran & O’Brien, 2017). Dermatological toxicities have also been reported in 2–27% of treated patients (Ransohoff & Kwong, 2017; Iberri et al, 2018), mainly mild-to-moderate rash, neutrophilic panniculitis, progressive hair and nail changes, skin infections, bruising, petechiae and purpuric eruption (Fabbro et al, 2015; Bitar et al, 2016; Ransohoff & Kwong, 2017; Iberri et al, 2018). In contrast, oral toxicity with ibrutinib has rarely been described. A prospective dermatological survey did not observe any mucosal involvement in a cohort of 66 consecutive patients (Bitar et al, 2016). However, a recent pivotal study reported all-grade and high-grade stomatitis in 11% and 1% of treated patients, respectively, but the clinical aspects were not documented (Byrd et al, 2014).

We report three patients (Table I) who progressively developed a grade ≥3 oral toxicity with ibrutinib monotherapy. Lesions were reminiscent of painful oral necrotic ulcers mimicking aphthous stomatitis and required treatment interruption in all cases. This case series is the first to report the clinical manifestations of grade ≥3 stomatitis induced by ibrutinib therapy.

The three patients, aged 66–78 years, were treated with oral ibrutinib (420 mg/day) as a monotherapy for the management of CLL. The time to onset of oral lesions ranged from 4 weeks to 16 months after ibrutinib initiation. Physical oral examination revealed necrotic progressive well-circumscribed mucosal ulcers of about 1 cm in diameter. They were surrounded by a brightly erythematous halo mimicking the appearance of major aphthous stomatitis. Lesions exclusively involved the nonkeratinized mucosa [tonsil, labial mucosa (Fig 1A)], ventral aspect of tongue (Fig 1B), and buccal mucosa in Patients 1 and 2 (Table I). Patient 3 (Table I) developed lesions on both nonkeratinized and keratinized mucosae, including multiple deep round ulcers on the tip and dorsal aspect of the tongue covered by a yellowish-grey pseudomembrane (Fig. 1C). All patients reported intense pain and dysphagia associated with recent weight loss. According to the National Cancer Institute Common Toxicity Criteria for Adverse Events v5.0 (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf), this oral toxicity was grade ≥3 and required interruption of ibrutinib.

Bacterial/fungal swab cultures and in situ polymerase chain reaction (PCR) screening for herpes simplex virus 1 and 2, varicella zoster virus and cytomegalovirus were negative in all cases. In addition, quantitative PCR in blood samples for Epstein–Barr Virus, parvovirus and human herpesvirus 6 were negative. Finally, no grade ≥2 neutropenia was noted.

The mucosal lesions rapidly resolved within a week in all patients after treatment discontinuation and supportive care including basic oral care, corticosteroids (prednisone mouthwash, topical application of clobetasol cream and/or systemic corticosteroids with prednisolone 1 mg/kg/day) (Fig 1D) and photobiomodulation (low-level laser therapy, power 150 mW; wavelength 660 nm, 4 J/cm²).

In one patient, a rechallenge with ibrutinib at the same dose (420 mg/day) resulted in the development of similar oral lesions within 5 days. Ibrutinib was therefore reinitiated at a lower dose (280 mg/day), without any recurrence. Similarly, ibrutinib was reinitiated at a lower dose (280 mg/day) in the other two patients without any recurrence of oral toxicity.

The clinical presentation of ibrutinib-associated stomatitis clearly differs from mucositis induced by chemotherapeutic agents, usually starting with distinct ulcers that ultimately become diffuse, poorly circumscribed and confluent. Moreover, chemo-induced mucositis appears 4–7 days after the first cycle (Vigarios et al, 2017) and solely involves nonkeratinized mucosae. Aphthous-like lesions on nonkeratinized mucosa have been previously reported with other therapies targeting different kinase pathways, especially mammalian target of rapamycin (mTOR) inhibitors. We also recently characterized similar mucosal involvement with several other tyrosine kinase inhibitors (TKIs) targeting human epidermal growth factor receptor (HER) (HER1–erlotinib, gefitinib, pan HER-afatinib, dacomitinib) or with multikinase angiogenesis inhibitors (sorafenib, sunitinib, pazopanib) (Vigarios et al, 2017).

The pathogenesis of ibrutinib-associated dermatological toxicities remains to be elucidated (Fabbro et al, 2015). It...
<table>
<thead>
<tr>
<th>Patient/sex/age (years)</th>
<th>Time to onset after ibrutinib introduction</th>
<th>Location of aphthous-like lesions</th>
<th>Stomatitis grade*</th>
<th>Other dermatological adverse events</th>
<th>ANC (×10⁹/l)†</th>
<th>Treatment</th>
<th>Clinical outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/male/66</td>
<td>16 months</td>
<td>Mainly located on the lip mucosa, tonsil and ventral aspect of the tongue (<em>nonkeratinized mucosa</em>)</td>
<td>4</td>
<td>_</td>
<td>1-6</td>
<td>Interruption of ibrutinib</td>
<td>Healing of oral mucosal lesions 3 days after ibrutinib interruption 2 weeks later, rechallenge at the same dose was followed by development of new similar mucosal lesions in 5 days Reintroduction at lower dose (280 mg/day) a few days later, without recurrence of oral lesions</td>
</tr>
<tr>
<td>2/female/66</td>
<td>4 weeks</td>
<td>Mainly located on the ventral aspect of the tongue and the buccal mucosa (<em>nonkeratinized mucosa</em>)</td>
<td>3</td>
<td>Grade 1–2 cutaneous ecchymotic lesions and follicular pustulosis on the limbs, with <em>Staphylococcus aureus</em> superinfection</td>
<td>1-45</td>
<td>Interruption of ibrutinib</td>
<td>Healing of mucosal lesions within 1 week Ibrutinib was reinitiated at lower dose (280 mg/day) without recurrence</td>
</tr>
<tr>
<td>3/female/78</td>
<td>7 months</td>
<td>Lesions developed on both <em>keratinized mucosa</em> (the dorsum and tip of the tongue) and <em>nonkeratinized mucosa</em> (ventral aspect of the tongue and the lip mucosa)</td>
<td>3/4</td>
<td>Grade 2 cutaneous ecchymotic lesions located on the limbs</td>
<td>3-3</td>
<td>Interruption of ibrutinib</td>
<td>Healing of mucosal lesions within 1 week Ibrutinib was reinitiated at lower dose (280 mg/day) without recurrence</td>
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†Absolute neutrophil count when stomatitis occurred.
would be reminiscent of a localized adaptive cellular immune response where ibrutinib-conjugated peptides would be presented to host immune cells via a major histocompatibility complex, leading to a T-cell-driven immune response and bystander tissue destruction (Fabbro et al., 2015). Moreover, although ibrutinib demonstrates high selectivity for BTK, it also exerts off-target effects on other kinases, including irreversible binding to epidermal growth factor receptor (EGFR) or HER2 (Bitar et al., 2016). This mechanism could partly explain the pathogenesis of ibrutinib-associated oral ulcers, even though anti-EGFR-related mucositis mostly occurs in the first weeks of treatment, solely involves nonkeratinized mucosae (similar to other kinase inhibitors, including mTOR inhibitors) and remains of low grade (Vigarios et al., 2017).

Oral aphthous-like ulcers have also been reported in haematological patients with concomitant neutropenia. However, no correlation with neutropenia could be established in our patients who presented a normal range of neutrophils (Table I). In addition, an infectious origin remains very unlikely, because the lesions clearly improved with corticosteroids and bacterial or viral swabs were negative in all cases.

In conclusion, ibrutinib can trigger severe impairing stomatitis that may require temporary discontinuation of the drug. Lesions can develop only after several months of treatment and can involve keratinized mucosa, which is unusual in comparison with the aphthous-like ulcers observed with other TKIs. In our experience, topical or short courses of systemic corticosteroids should be recommended for managing oral ulcers and relieving pain, once an active infection has been ruled out. The clinical outcomes observed in our patients suggest that ibrutinib may be resumed at a lower dose, without any recurrence.

Declarations

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References


