Severe Maculopapular Exanthema Induced by Regorafenib: Successful Desensitization and Adaptation of a Dosage Regimen

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Regorafenib is an oral protein kinase inhibitor approved for the treatment of hepatocellular carcinoma, metastatic colorectal cancer, and stromal tumors. The recommended dose is 160 mg/d for 3 weeks followed by 1 week off therapy (resting week). Hand-foot skin reaction, mild rash, and mucositis are common mucocutaneous adverse effects frequently requiring dose modification [1]. Severe skin reactions such as erythema multiforme or Steven-Johnson syndrome may preclude further administration [2-3]. There are no published data on desensitization to regorafenib.

A 58-year-old woman diagnosed with metastatic hepatocellular carcinoma, was treated with sorafenib followed by nivolumab-ipilimumab. Given the progression of her disease, she started third-line therapy with regorafenib 160 mg/d, decreasing to 120 mg/d on day 10 owing to oral mucositis. On day 12, she developed fever (39ºC) and took acetaminophen and amoxicillin (for the fifth time during the previous months owing to recurrent high fever of unknown origin, probably neoplastic fever). On day 16, she was admitted to hospital with a pruritic generalized maculopapular rash (Supplementary Figure, A), vaginal and conjunctival erythema, and persistent high-grade fever. There were no corneal or genital ulcers, blisters or epidermal detachment. The blood work-up showed no eosinophilia or increase in liver transaminases. Regorafenib, acetaminophen, and amoxicillin were discontinued. Intravenous antihistamines and corticosteroids were initiated. The fever subsided and the exanthema improved markedly in 24 hours, resolving within 1 week. The skin biopsy revealed extensive vacuolar degeneration of the basal layer, necrotic basal keratinocytes, and a dermal perivascular lymphocytic inflammatory infiltrate with scarce eosinophils (Supplementary Figure, B). The results of serology testing for cytomegalovirus, Epstein-Barr

virus, and *Mycoplasma pneumoniae* and blood cultures were negative. The patient was discharged, and corticosteroids were tapered. α-Fetoprotein decreased from 15 323 to 3 866 µg/L. Since regorafenib was the only therapeutic option available, desensitization was scheduled in 2 weeks. The patient was informed about the benefits and potential risks of desensitization and signed the appropriate consent form.

Given the severity of the reaction, the dose of regorafenib was reduced to 80 mg/d for the first desensitization. Based on a previous protocol for sorafenib [4], a 10-step protocol was followed, reaching a cumulative dose of 80 mg on day 1 (Table). Temperature, skin signs, eosinophilia, and liver function were monitored. Five hours later, the patient developed a mild pruritic generalized erythematous rash. Antihistamines and corticosteroids were administered, with complete resolution within 15 hours. On the following days, the dose was reduced before being slowly increased to 80 mg, with no further adverse events (Table). The patient was discharged and continued to take 80 mg/d for 3 weeks followed by 1 week off treatment.

The results of patch testing with regorafenib (0.1%-1%) and sorafenib (0.1%-1%-10%, pet) during the week off regorafenib, 3 weeks after receiving corticosteroids (see above), were negative.

A second desensitization was performed the following week. A dose of 80 mg was reached on day 1 (same 10-step protocol). The doses reached on days 2 and 3 (single doses) were 100 mg and 120 mg, respectively. All doses were well tolerated. The patient continued to take 120 mg daily. In order to avoid monthly desensitization and hospitalization and after consultation with the hepatologist, we decided to continue with 120 mg/d for 3 weeks, decreasing to 80 mg during the resting week instead of discontinuation, in order to maintain desensitization. Potential drug toxicity was closely monitored, and the dose was adjusted accordingly.

Four months later, the results of intradermal tests with acetaminophen, penicilloyl polylysine, minor determinant mixture, penicillin G, and amoxicillin were negative, as were those of controlled challenge tests with acetaminophen and amoxicillin.

At this point, the patient had completed 1 year of regorafenib. α-Fetoprotein was 1623 µg/L. Periodic computed tomography showed stability of pulmonary lesions and no relapse of liver disease for months. However, the most recent scan showed a slight increase in the size of the pulmonary lesions, with new pulmonary nodules suggestive of metastasis. The dose of regorafenib was increased to 160 mg/d and has since been well tolerated.

Although the development of targeted therapies such as protein kinase inhibitors has revolutionized cancer treatment, effective therapeutic options remain limited for most tumors. In this scenario, drug hypersensitivity is a potential barrier to treatment. Fortunately, drug desensitization provides an effective tool not only in immediate hypersensitivity reactions, but also in delayed hypersensitivity reactions [5-7]. Several successful rapid and slow desensitization protocols for protein kinase inhibitors have been reported [4,5,8,9], although, to date, not for regorafenib.

It is worth highlighting that, according to guidelines, patients with severe cutaneous adverse reactions such as Steven-Johnson syndrome, toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms should not undergo desensitization given the high risk of a severe or even fatal reaction, and the rationale for desensitization remains unclear [6,7]. The difficult clinical decision to undertake a desensitization protocol in this case was based on the absence of an alternative treatment that would extend the patient's life expectancy. On the other hand, the patient did not have skin detachment, mucosal ulcers, eosinophilia, or internal organ damage, which would contraindicate desensitization, and the exanthema markedly improved with corticosteroids in 24 hours. Desensitization techniques should be performed only by an expert allergist in an area of the hospital that is equipped to manage severe reactions. Close monitoring for the presence of fever, eosinophilia, liver damage, and damage to any other organ is required in the case of delayed reactions. Furthermore, it must be taken into account that drug desensitization protocols for delayed reactions and premedication are empirical, the underlying mechanism is unknown, there are no supporting in vitro data (in contrast with immediate reactions), and published experience remains limited.

Regorafenib was reintroduced through desensitization to minimize the risk of eliciting a severe cutaneous adverse reaction. Since the patient experienced a mild rash following desensitization to regorafenib, it was subsequently decided to rule out hypersensitivity to acetaminophen and amoxicillin.

The patient could have been sensitized to regorafenib by previous exposure to sorafenib, which is structurally related. However, the negative patch test results do not confirm this hypothesis.

Table. Rapid 10-Step Desensitization Protocol (Day 1)[a]

Day/Cumulative Dose	Dose, mg	Time Interval	Reaction
D1[b] 10-Step desensitization protocol: 80 mg	0.08	15 min	No
	0.16		No
	0.32		No
	0.64		No
	1.28		No
	2.56		No
	4.96		No
	10		No
	20		No
	40		Mild erythematous rash 5 h later
D2/30 mg	10-10-10	3 h	No
D3/40 mg	10-10-20	3 h	No
D4/50 mg	10-20-20	3 h	No
D5/60 mg	20-20-20	3 h	No
D6/80 mg	40-40	3 h	No
D7/80 mg	80	-	No

[a]A mild skin reaction developed 5 hours later. The dose was reduced and increased carefully over the following days.
[b]Premedication with intravenous methylprednisolone (20 mg) and dexchlorpheniramine (5 mg).

This is the first report of successful desensitization to regorafenib, which enabled the patient to be treated with the only therapeutic option available. Moreover, multidisciplinary management involving allergists and hepatologists made it possible to modify the standard dosage regimen in order to avoid drug discontinuation and thus maintain desensitization while preventing risks and multiple hospitalizations.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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