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To the Editor,

Paraneoplastic pruritus represents a frequent symptom in the debut or progression of lymphoproliferative disorders. It affects approximately 30% of patients with Hodgkin lymphoma and 15% of patients with non-Hodgkin lymphoma(1). Aprepitant has shown promising results in the treatment of refractory pruritus of primary cutaneous T-cell lymphomas (CTCL)(2-4). However, its effect on paraneoplastic pruritus of systemic lymphoproliferative disorders has been poorly documented. In order to evaluate its possible usefulness in this subgroup of patients, a retrospective study of the cases treated in our center was carried out from March 2017 to June 2019. All patients were informed about the characteristics of the treatment, its use outside the authorized indication and consent was given in order to initiate it. The intensity of pruritus was evaluated using a quantitative numerical scale (from 0: no pruritus, to 10: the worst imaginable pruritus), obtained before starting treatment, after the first week of aprepitant and monthly follow-up. The recall gap of pruritus measurement was 24 hours. There were 6 patients, 4 men and 2 women, with an average age of 64.5 years (32-87). Table 1 summarizes the clinical characteristics for each patient. The baseline itch score ranged from 6 to 10 (mean 8.2). In all cases an initial regimen of aprepitant 125mg, 80mg, 80mg was administered on three consecutive days to assess the response to the drug and its tolerance. Subsequently, 2 cases continued with the same weekly pattern and 2 patients at a biweekly dose of 125mg, 80mg, 80mg. 4 patients achieved a reduction in pruritus intensity of 3 or more points (3 to 7 points, mean 4) and night rest improved in 4 subjects (2 patients stopped hypnotic drugs). The best response to the drug was experienced at night, when those patients who could not sleep began to rest after the drug was administered. Table 2 describes treatment regimens and their impact on pruritus. No side effects or drug interactions were documented. Aprepitant is a neurokinin 1(NK1) receptor antagonist indicated in the prevention of acute and deferred nausea and vomiting associated with chemotherapy. Its antipruritic effect seems to be related to the blockade of substance P, a NK1 receptor ligand, described as an important mediator of pruritus development and maintenance. It was first used as an antipruritic drug in cancer patients in 2009, in 3 patients with Sézary syndrome, at a dose of 80mg daily(5). Subsequently several guidelines have been published in patients with CTCL. In the context of systemic lymphomas there is only one publication in a patient with Hodgkin lymphoma who responded satisfactorily to a dose of 80mg daily(6). Factors that would contribute to a better response to the drug have been studied in patients with CTCL. It seems that the extension and type

of skin lesions would help to a better response, being higher in non-erythrodermic patients(7). In our series, all patients with a satisfactory response to aprepitant had secondary skin involvement (1 at onset of disease, 2 at progression) or in the context of favored cGVHD during relapse. This would reinforce the hypothesis that skin plays an important role in the anti-pruritic effect of NK1 receptor antagonists. In summary, in our case series, aprepitant has been used as an effective therapeutic alternative in refractory pruritus of patients with systemic lymphoproliferative disorders without other options. The effect appears to be superior in cases where secondary skin lesions are present. However, despite these favorable results, this study has several limitations, as it is a small, retrospective case series that lacks a control group. Future studies are needed to evaluate the efficacy of aprepitant in the treatment of paraneoplastic pruritus in systemic lymphomas.

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Table 1: Clinical features of patients treated with aprepitant

Table 2: Itch scores, treatment regimens and follow-up of patients

Patient	Age/sex (M/F)	Diagnosis	Previous anti-itch treatment	Disease-specific treatment	Skin involvement
1	87/M	Peripheral T-cell lymhoma, NOS	Hydroxycine, dexchlorpheniramine, prednisone, methylprednisolone, phototherapy	Methotrexate	Erythematous plaques and papules (specific secondary skin involvement)
2	32/M	Hodgkin lymphoma	Dexchlorpheniramine, ebastine, prednisone, methylprednisolone, naltrexone, sertraline, phototherapy	Bendamustine	cGVHD
3	75/M	Angioimmunoblastic T-cell lymhoma	Dexchlorpheniramine, hydroxycine, prednisone, methylprednisolone	Cyclophosphamide, etoposide, procarbazine, prednisone	Erythematous plaques (specific secondary skin involvement)
4	55/F	Hodgkin lymphoma	Dexchlorpheniramine, hydroxycine, cetirizine, prednisone, phototherapy	No	No
5	79/F	Angioimmunoblastic T-cell lymhoma	Dexchlorpheniramine, hydroxycine, prednisone, phototherapy	No	Maculopapular eruption (non-neoplastic skin involvement at diagnosis)
6	59/M	Follicular lymhoma	Hydroxycine, cetirizine, phototherapy	No	No

cGVHD: chronic graft versus host disease

NOS: Not Otherwise Specified

Patient	Baseline itch score (0-10)	Nocturnal rest	Initial dose of aprepitant (mg/day)	Itch score after first dose of aprepitant (0-10)	Nocturnal rest after first dose of aprepitant	Continuation dosage (changes in dosage until disease progression* or death#)
1	8	Cannot sleep	125, 80,80	1	Sleeps almost all night	125,80,80 weekly, 4 weeks* 40mg daily, 4 months#
2	8	Cannot sleep	125, 80,80	4	Sleeps all night (stopped zolpidem)	125mg,80mg,80mg biweekly, 6 weeks* 40mg daily, 4 weeks* 80mg daily, 6 weeks#
3	8	Cannot sleep	125, 80,80	4	Moderate nocturnal rest (less agitation)	125,80,80 weekly, 2 weeks#
4	9	Cannot sleep	125, 80,80	9	Cannot sleep	
5	10	Cannot sleep	125, 80,80	7	Sleeps almost all night (stopped lorazepam)	125mg,80mg,80mg biweekly, 3 weeks* 40mg daily, 3 weeks*
6	6	No sleep loss	125, 80,80	6	No sleep loss	