Incidence, Characteristics, and Management of Alpelisib-Associated Rash in Patients With Advanced Breast Cancer

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Synopsis

- Hormone receptor-positive (HR+), human epidermal growth factor receptor-2–negative (HER2–) breast cancer is the most common subtype of advanced breast cancer (ABC).[1]
- ~40% of patients with HR+, HER2– breast cancer have mutations in the *PIK3CA* gene, which encodes the α subunit of phosphatidylinositol-3-kinase (PI3K).[2-4]
  - *PIK3CA* mutations have been associated with the development of resistance to endocrine therapy, and are a negative prognostic factor in ABC.[4,5]
- Alpelisib is an α-selective PI3K inhibitor approved in combination with fulvestrant for the treatment of patients with HR+, HER2– ABC with mutations in the *PIK3CA* gene who progressed on or after endocrine therapy.[6]
  - U.S. Food & Drug Administration (FDA) approval of this combination was based on improved efficacy data compared with placebo plus fulvestrant, and a manageable safety profile reported in the Phase III SOLAR-1 trial (NCT02437318).[7]
- Cutaneous toxicities, particularly the development of rash, are a class effect of PI3K pathway inhibitors and have been reported in up to 54% of patients treated with alpelisib.[7-9]

Objective

- The objective of this poster is to provide dermatologists with specific guidance on the management of alpelisib-associated dermatologic adverse events.

Methods

- This review of alpelisib-associated rash includes safety data from the SOLAR-1 trial, the BYLieve study, and a single-center retrospective study.
  - SOLAR-1 evaluated alpelisib (300 mg QD) + fulvestrant (500 mg, every 28 days and once on day 15) or placebo + fulvestrant (equal dosing) in women or men with HR+, HER2– ABC who had progressed on or after prior aromatase inhibitor (N=572).[7]
  - BYLieve (NCT03056755), is an ongoing Phase II study evaluating alpelisib (300 mg QD) + fulvestrant (500 mg, every 28 days and once on day 15) or letrozole (2.5 mg QD) in women of any menopausal status and men with HR+, HER2– ABC and confirmed *PIK3CA*-mutant status who had progressed on or after prior treatments.[10]
    - Results from Cohort A (N=127; cohort of patients previously treated with cyclin-dependent kinase [CDK]4/6 inhibitors) have recently been reported and are included here.
  - A single-center retrospective study evaluated data from 4 randomized trials and postapproval treatment records involving ABC patients who received alpelisib-based treatments (most frequently combined with endocrine therapy; N=102), with the purpose of characterizing alpelisib-associated cutaneous toxicities and describing management strategies.[11]
- Alpelisib prescribing information and other available literature are also included.

Results

Incidence of Alpelisib-Associated Rash

- Clinical trials have reported an incidence of any-grade rash (by single preferred term) ranging from 28% to 36% (grade ≥3 = 9%-10%) in alpelisib-treated patients.[7,10]
  - Rash led to treatment discontinuation in 3% to 4% of these patients.
  - No grade 4 rash was reported in SOLAR-1 or in the retrospective study.[7,9,11]

Characteristics of Rash

- In clinical studies, the median time to rash onset was approximately 2 weeks after starting alpelisib treatment.[9,11]
- In the retrospective study, median duration of rash was 7 days.[11]
  - In SOLAR-1, the median time to improvement by at least 1 grade in patients with grade ≥3 rash was 11 days.[9]
- Rash is more frequently localized in the trunk (including chest, abdomen, and back) and extremities; rash on face and scalp is less common.[11]
- Rash events can be asymptomatic, or present symptoms such as burning pain or pruritus (more common in grade 3 rash).[11]
- The vast majority of patients who develop alpelisib-associated rash present with maculopapular (morbilliform) rash; acneiform rash can also be observed. Characteristics of these 2 rash types are presented in **Table 1**.[11]
- Retrospective data from 2 patients who experienced alpelisib-associated rash showed histology consistent with a hypersensitivity reaction.[11]
- Laboratory assessment data showed that patients who developed rash had an increase in blood eosinophils after 2 weeks of alpelisib treatment compared with baseline (2.7% vs 4.4%, $P<0.05$); a trend toward elevated ALT was also observed.[11]
  - No differences in lymphocyte, neutrophil, or monocyte counts were reported between patients who developed rash and those who did not.

Table 1. Characteristics of alpelisib-associated rash

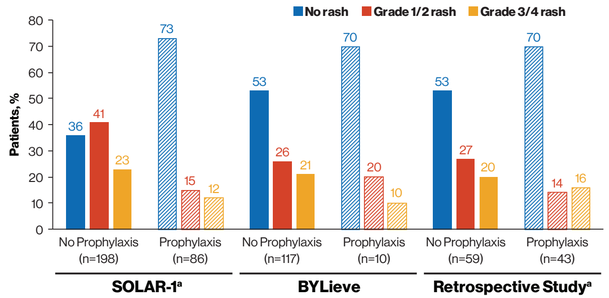
Rash Type	Relative Incidence[11]	Possible Symptoms[11-13]	Clinical Features[11-15]	Histopathological Characterization[11,16]
Maculopapular (morbilliform)	26 of 29 patients in the alpelisib retrospective study (90%) experienced maculopapular rash; more common in patients receiving alpelisib plus hormone therapy	• Pruritic • Burning sensation • Tightness	• Presence of macules and papules • Centripetal distribution; mostly localized on upper trunk and extremities	• Superficial perivascular dermatitis with focal or mild interface change or folliculocentric spongiosis • May present with lymphocytic infiltration
Acneiform	3 of 29 patients in the alpelisib retrospective study (10%) experienced acneiform rash; more common in patients with HER2+ BC receiving alpelisib plus trastuzumab and anti-HER3 Ab	• Generally asymptomatic; however, pruritus and tenderness may occur	• Presence of papules or pustules • Wide distribution; frequently located on face, scalp, upper chest, and back • Presence of open comedones has been observed with everolimus, which inhibits another node of the PI3K pathway (mTOR)	• Histopathology for alpelisib-associated acneiform rash not reported • Patients treated with everolimus have presented with eczematous histology, interface dermatitis, and spongiosis

Ab, antibody; BC, breast cancer; HER, human epidermal growth factor receptor; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase.

Prevention of Alpelisib-Associated Rash

- Administering prophylactic medication to patients receiving alpelisib before the onset of rash has been shown to reduce the incidence and severity of this adverse event (**Figure 1**).[9-11]

Figure 1. Occurrence of rash in patients who received prophylaxis and those who did not



[a]No grade 4 rash was reported in SOLAR-1 or in the retrospective study.

- Strategies that both health care professionals (HCPs) and patients can adopt to prevent the onset of alpelisib-associated rash are described in **Figure 2**.[9-11]

Figure 2. Rash prevention strategies

HCPs

- Consider prescribing prophylactic nonsedating antihistamines (10 mg/day cetirizine or loratadine) to patients starting alpelisib during the first 8 weeks of therapy.
- Educate patients on the signs and symptoms of alpelisib-associated rash for early-reporting and prompt management.

Patients

- Maintain proper skin hydration.
- Avoid sun exposure and irritant skin products to prevent worsening of rash, dryness, and itching.

Management of Alpelisib-Associated Rash

- Alpelisib-associated rash is generally reversible with adequate co-medication and, if needed, alpelisib dose adjustments/interruption (mostly in patients experiencing grade 3 rash; **Figure 3**).[7,11]
  - Retrospective data showed that upon improvement to grade ≤1 rash, 12 of 16 patients (75%) who interrupted treatment were able to resume alpelisib and did not experience rash recurrence (9 of those patients were rechallenged with the initial alpelisib dose); 4 patients (25%) experienced rash recurrence within 24 hours of alpelisib rechallenge and required permanent alpelisib discontinuation.[11]
- Active management of alpelisib-associated rash may help limit dose adjustments and prevent treatment interruptions to achieve better therapeutic efficacy.[9,11]
- Management strategies include
  - Early identification and intervention
  - Patient education
  - Clear guidance on preventive treatment
  - HCP training on supportive medications and dose adjustment protocols
- In SOLAR-1, more detailed management guidelines introduced after a protocol amendment resulted in a decrease in incidence of grade 3 rash.[9]

Figure 3. Management of alpelisib-associated rash based on severity[6,7,11,17,18,a]

CTCAE grading	Grade 1 <10% BSA with active skin toxicity.	Grade 2 10%-30% BSA with active skin toxicity.	Grade 3 30% BSA with active skin toxicity.	Grade 4 Life-threatening; any % BSA with extensive superinfection and IV antibiotics indicated.
Alpelisib dosing	No alpelisib dose adjustment required.		Interrupt alpelisib until improved to grade ≤1.	Permanently discontinue alpelisib.
Supporting medication	Initiate class I-III topical corticosteroids (triamcinolone, betamethasone, clobetasol, or fluocinonide). • If presenting with pruritus or burning sensation, add antihistamines in the morning (nonsedating: cetirizine/loratadine) and at night (sedating: hydroxyzine or diphenhydramine). • If presenting with acneiform rash, consider other causative agents (oral contraceptives, antiandrogen medications, dehydroepiandrosterone, etc); avoid diphenhydramine.		Follow grade 1/2 supporting medication, and initiate systemic corticosteroids[b] (prednisone[c], 10-14 days with taper).	
Alpelisib rechallenge	Alpelisib may be resumed at the same dose once rash resolves to grade ≤1, or at a reduced dose at second occurrence. A graded rechallenge with alpelisib may also be considered while maintaining antihistamine treatment and tapering systemic steroids.			

[a]Evaluation by a dermatologist familiar with these toxicities is recommended.
[b]Systemic corticosteroids may worsen alpelisib-associated hyperglycemia. Caution should be exercised.[19]
[c]Methylprednisolone or prednisolone are preferred over prednisone for patients with liver disease.
BSA, body surface area; CTCAE, Common Terminology Criteria for Adverse Events; IV, intravenous.

Severe Cutaneous Reactions

- Life-threatening skin toxicities, such as Stevens-Johnson syndrome (SJS), erythema multiforme (EM), drug reaction with eosinophilia and systemic symptoms (DRESS), and toxic epidermal necrolysis (TEN) are not common.[6,11]
  - Patients with a history of severe cutaneous reactions should not start alpelisib treatment.[6]
  - Symptoms may include a prodrome of fever, flu-like symptoms, mucosal lesions, or progressive skin rash.[6]
  - Alpelisib should be interrupted if severe cutaneous reactions are suspected, and permanently discontinued if diagnosis is confirmed or grade 4 rash occurs.[6]

Conclusions

- Rash is a frequently observed alpelisib-associated adverse event that can be managed with medication, such as antihistamines and corticosteroids, and alpelisib dose adjustments and interruptions.
  - Rash leading to alpelisib treatment discontinuation did not occur frequently in clinical studies and most patients were able to resume anticancer treatment upon rash resolution.
- Preventive strategies, such as administration of prophylactic medication, patient education, early detection of symptoms, and prompt treatment, may help minimize the onset and severity of alpelisib-associated rash.
- Severe cutaneous reactions (SJS, EM, DRESS, and TEN) are not common in patients treated with alpelisib; if suspected, alpelisib should be interrupted, and permanently discontinued if diagnosis is confirmed.

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