

Gezondheids**Zorg** met een Ziel

# NECTIN-4-DIRECTED ONCOLOGIC THERAPIES, WHAT TO EXPECT AS A DERMATOLOGIST? Meulewaeter E<sup>1</sup>, Temmerman L<sup>1</sup>

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## CASES

- A 70-year-old male with lymphatic metastasized urothelial carcinoma treated with enfortumab vedotin develops itchy erythematous papules on the chest two weeks after treatment initiation.
  Skin biopsy shows apoptotic keratinocytes, focal interface dermatitis and a high number of mitoses.
  Regression is seen with application of Mometasone Furoate 1mg/g cream.
- A 65-year-old male with bone metastases of a transitional cell carcinoma treated with enfortumab vedotin. Two weeks after treatment initiation, bright erythema and blister formation with Nikolsky sign arises in all flexural areas. Skin biopsy shows interface dermatitis and numerous mitoses.



Regression is seen after enfortumab vedotin was stopped.

#### WHAT IS ENFORTUMAB VEDOTIN

- A monoclonal antibody conjugated to monomethyl auristatin E (MMAE), that targets Nectin-4, resulting in apoptotic death of tumor cells
- Nectin-4 is an immunoglobulin-like adhesion molecule that is expressed in the transitional **epithelium of the bladder**, epidermal **keratinocytes** and skin appendages
- Overexpression of Nectin-4 in several tumors is associated with **disease progression** and poor survival, which makes Nectin-4 an interesting target in the treatment
  - New therapy for patients with locally advanced or metastatic urothelial cancer
  - Possible future implementation of Nectin-4 inhibition in the treatment of cutaneous squamous cell carcinomas

### **CUTANEOUS SIDE EFFECTS**

- While Nectin-4 is expressed in normal keratinocytes, dermatologic side effects can be expected
- Cutaneous adverse drug reactions were reported in approximately one third of treated patients.

Figure 1. Case 1: erythematous papules in the truncal region



- Onset most often within the **first cycle** of treatment
- Diverse cutaneous adverse events
  - Erythematous, scaly, pruritic papules in the flexural and acral areas and trunk
  - Possible severe cutaneous adverse events: Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP)
- **Conjunctivitis, stomatitis or fever** can be present simultaneously
- Histopathologic features include vacuolar interface dermatitis, starburst mitotic features and maturation disarray of epidermal keratinocytes

# **MANAGEMENT OF CUTANEOUS EVENTS**

- Prophylaxis by **barrier-protecting agents** and application of **sunscreen**
- Mild-to-moderate symptoms: **topical corticosteroids**, combined with **topical antibiotics** for the intertriginous areas
- Severe events: Dose holds or dose reduction ± oral corticosteroids

*Figure 2.* Histopathology: acantholysis, hyperkeratosis, <u>mitoses</u>, apoptotic keratinocytes and interface dermatitis. (Picture and analysis by Dr. Lambert I., Dermpat, Belgium)



- When SJS/TEN is suspected, enfortumab vedotin should be suspended instantly

## TAKE HOME MESSAGES

- Nectin-4 is a **new target** for treating urothelial carcinoma, and may be a target for treating cutaneous squamous cell carcinoma in the future
- Nectin-4 is expressed in normal keratinocytes, so diverse cutaneous adverse events will be seen
- Histopathology typically shows numerous **mitotic** features
- Some cutaneous adverse events are typical and need to be recognized by dermatologists

Figure 3. Case 2: bright erythema and blister formation in the left axilla

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