NEW DRUGS

Talimogene laherparepvec

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Approved indication: melanoma

Imlygic (Amgen)
vials containing 10^6 or 10^8 plaque-forming units/mL for injection

Talimogene is an oncolytic immunotherapy for melanoma consisting of genetically modified herpes simplex virus 1. It is indicated for intralesional treatment of cutaneous, subcutaneous and nodal lesions (after initial surgery) that cannot be surgically removed.

The pathogenicity of the virus has been attenuated by removing neurovirulence genes. These have been replaced by sequences encoding cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF). Once the virus is injected into a lesion, it is thought to multiply within cells and cause tumour lysis. The virus also causes local production of GM-CSF which is believed to stimulate the immune system to target melanoma cells. Talimogene can infect healthy cells but it is designed not to multiply inside them.

The approval of talimogene is based on a pivotal open-label phase III comparative trial with subcutaneous GM-CSF in 436 patients with inoperable stage III or IV melanoma. Those randomised to talimogene were given an initial dose containing 10^6 plaque-forming units (PFU)/mL. This was followed by a 10^8 PFU/mL dose three weeks later which was then continued every two weeks. Patients in the comparator group received recombinant GM-CSF 125 microgram/m^2 given subcutaneously every day for 14 days of a 28-day repeating cycle. Both treatments were continued for six months regardless of disease progression. Median duration of treatment was 23 weeks for talimogene and 10 weeks for GM-CSF. More patients had a durable response to talimogene than to GM-CSF (16.3% vs 2.1%). Median overall survival was also longer with talimogene than with the comparator (23.3 months vs 18.9 months) but the difference was not statistically significant (see Table).[1]

An earlier open-label, single-arm phase II trial in 50 patients with metastatic melanoma provided supporting data for the approval of talimogene. After a similar talimogene regimen was administered, 13 patients had a complete or partial response.[2]

The most common adverse events with talimogene were fatigue (50.3% of patients), chills (48.6%), pyrexia (42.8%), nausea (35.6%), flu-like illness (30.5%), injection-site pain (27.7%) and vomiting (21.2%). Most of these were mild to moderate.[1]

Impaired healing can occur at injection sites, particularly in those with underlying risks such as previous radiation treatment or lesions at poorly vascularised areas. Treatment-related cellulitis at the injection site was reported in 3.1% of patients. Talimogene can cause immune-mediated effects such as glomerulonephritis, vasculitis and pneumonitis. Worsening psoriasis and vitiligo have also been observed in patients during treatment.

As this drug contains live virus, it has the potential to cause disseminated herpetic infection in immunocompromised patients, such as those taking long-term, high-dose steroids. The drug is contraindicated in severely immunocompromised patients.

Table **Efficacy of talimogene for inoperable grade III or IV melanoma in a phase III trial**

Outcome	Talimogene (295 patients)	GM-CSF (141 patients)
Durable response rate*	16.3%	2.1%
Complete responses	32 (10.8%)	1 (<1%)
Partial responses	46 (15.6%)	7 (5%)
Median time to treatment failure	8.2 months (CI 6.5–9.9)	2.9 months (CI 2.8–4)
Median overall survival	23.3 months (CI 19.5–29.6)	18.9 months (CI 16–23.7)
Estimated survival after 4 years	33%	21%

* primary end point defined as the percentage of patients with a complete or partial response lasting for at least six months continuously and beginning within the first 12 months of treatment
CI confidence interval
GM-CSF granulocyte-macrophage colony-stimulating factor
Source: Reference 1

Patients treated with talimogene have been found to shed live virus. To avoid transmission, close contacts including family members, sexual partners and healthcare professionals should avoid direct contact with injected lesions and body fluids from the patient. In particular, patient contact with infants, pregnant women and people who are immunocompromised is not recommended. Patients should be warned that touching and scratching injection sites can spread the virus to other parts of the body. Suspected herpetic infections in patients or close contacts should be reported to the doctor.

There have been no studies on drug interactions with talimogene. However, co-administration of aciclovir and other antivirals could interfere with the efficacy of talimogene.

Numerous lesions can be injected at each treatment visit with the largest lesions injected first. The recommended injection volume depends on the size of the lesion. No more than 4 mL in total should be used at each consultation. Pregnant or immunocompromised healthcare providers should not handle or administer talimogene.

Although intralesional injections of talimogene were significantly better than subcutaneous GM-CSF for melanoma, the effect was modest with only 1 in 6 patients having a durable response. It is unclear why subcutaneous GM-CSF was chosen as the comparator in the main trial as there have been inconsistent results for this regimen in patients with melanoma.[3]

It is not known how talimogene will compare with other approved treatments for melanoma, such as pembrolizumab, nivolumab and ipilimumab.

[X] manufacturer did not respond to request for data

REFERENCES

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The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, the European Medicines Agency and the Therapeutic Goods Administration.