Research letter

Topical diphencyprone for the treatment of locoregional intralymphatic melanoma metastases of the skin; the 5-year Norwich experience

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Dear Editor, Locoregional intralymphatic melanoma metastases (LIMMs) (in-transit or satellite metastases) of the skin can present a significant management challenge to the melanoma clinician across all specialties. Up to 12% of all patients with melanoma will develop LIMMs of the skin.[1–4] The clinical manifestation of this problem can be very heterogeneous. LIMMs present as erythematous or pigmented nodules ranging in size from 0·2 to 2 cm. They can be located anywhere in the affected region, from the superficial intradermal lymphatics to the deep soft tissues, including fat and muscle. They may present as single, large lesions or numerous superficial papules. The lesions may appear infrequently over a prolonged period of follow-up or rapidly in simultaneous clusters throughout the affected region.

Many factors are associated with the development of LIMMs, particularly high-risk features of the primary tumour, such as increasing Breslow thickness, lymphovascular invasion and ulceration, in addition to the presence of regional lymph node involvement.[5,6] The anatomical site of the primary tumour is also important – LIMMs are commoner when the primary tumour is on the lower extremities compared with the head and neck.[3,7] The onset of LIMMs is associated with a poor prognosis and often precedes the onset of systemic disease.[8] The 5-year survival for these patients is 32–69%;[8] however, there remains a significant proportion of these patients who survive a long time with no further disease progression. Therefore, it is important that effective treatment strategies are implemented for long-term palliation of these patients to avoid undue morbidity for patients who are often otherwise asymptomatic.

Given the highly variable manifestation of this clinical problem, it is not surprising that many treatments are currently recommended for LIMMs. Where single or limited numbers of LIMMs are present, surgical resection or CO_2 laser ablation is usually the treatment of choice. However, where multiple lesions are present, local therapies are usually offered, namely topical treatments such as imiquimod, or intralesional treatments including Bacille Calmette–Guérin, rose bengal, interleukin-2, electrochemotherapy and talimogene laherparepvec (T-VEC). Regional chemotherapy such as isolated limb infusion may be used for more extensive metastases of a limb. Systemic therapy may be indicated for extensive involvement.

Effective treatment of LIMMs of the skin using topical diphencyprone (DPCP) has been described previously.[9–11] Complete and partial response rates of 46% and 38%, respectively, have been recently reported from Australia.[11] Our skin tumour unit is a quaternary referral centre for isolated limb infusion (ILI); accordingly we review a large cohort of patients with LIMMs. We developed our DPCP service in parallel with our regional chemotherapy service with a view to offering an alternative method of palliation for patients with low-volume disease. Many of the patients treated with topical DPCP had been referred to our centre for consideration of ILI. As our initial experience with topical DPCP demonstrated that it was effective in treating smaller, more superficial LIMMs, we offered this as a less morbid alternative to ILI. Here we provide the first U.K. report, derived from our prospectively recorded experience in treating 35 patients with LIMMs of the skin with topical DPCP between March 2010 and March 2015.

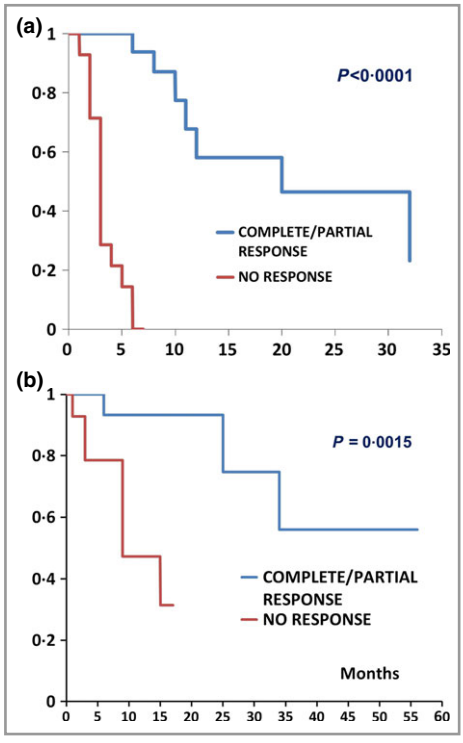

Fig 1. Responders vs. nonresponders: (a) progression-free survival; (b) overall survival.

Between March 2010 and March 2015, 35 adult patients, 16 males and 19 females, with biopsy-proven LIMMs were assessed and treated with topical DPCP. The mean age was 74 (range 53–95) years. Typically, patients with multiple, unresectable, small metastatic deposits of melanoma with superficial disease, usually located in the dermis and subcutis, were offered the treatment. Seventeen patients had disease of the lower limb but the face and torso were also treated (11 patients). Patients were sensitized to 2% DPCP in acetone – this was applied to the inner aspect of the arm using a Finn chamber which was left in place for 48 h. This elicited an eczematous reaction in all patients 2–5 days post application. Treatment with once-weekly applications of cream was started 7–10 days later. The initial concentration was 0·005% in aqueous cream and this was titrated to achieve a moderate eczematous reaction.[9] The concentration of DPCP used varied from 0·000001% to 0·05%. Side-effects were uncommon, usually severe eczema requiring modification of the dose. Patients who responded to the treatment continued the cream but those whose disease progressed discontinued the cream.

Patients were reviewed clinically at approximately 6–8-week intervals. The treatment response was assessed and recorded photographically by the senior author (J.G.). Ten patients (28·6%) had a complete response with complete resolution of their LIMMs; 11 patients (31·4%) had a partial response defined as reduction or resolution of some but not all LIMMs (five patients) and/or significant slowing of the rate of disease progression with no extension beyond the area being treated (six patients);[11] 14 patients (40%) had no response. The median follow-up was 9 (range 1–56) months. Nine (25·7%) have since died of their disease. None of the patients with a complete response have relapsed to date. Relapse or progression of LIMMs was significantly associated with reduced progression-free survival ($P < 0·0001$) and overall survival ($P = 0·0015$) (Fig. 1a,b).

DPCP is a well-known potent contact sensitizer that can induce contact hypersensitivity reactions in approximately 98% of people.[12] The mechanisms of action on melanoma are unknown. DPCP is a hapten, which induces delayed-type hypersensitivity reactions. DPCP-specific induced cytokines include interleukin (IL)-24 and IL-9, which are tumour-suppressor cytokines with known melanoma activity.[13]

Our results are encouraging and would indicate that topical DPCP is effective in treating LIMMs of the skin. The response rates seen in our cohort, which is one of the largest to report to date, compare favourably with other locoregional treatments. The main advantages of DPCP are that it is inexpensive (costing in the region of £90 per month per patient), easy to use, well tolerated and can be applied to treat large areas of the skin. In addition, the psychological benefits of self-directed therapy should not be underestimated.

Further work is required to understand the mechanisms by which DPCP results in resolution of LIMMs of the skin.

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