Journal Pre-proof

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PII: S1748-6815(20)30133-9
DOI: https://doi.org/10.1016/j.bjps.2020.03.007
Reference: PRAS 6480

To appear in: *Journal of Plastic, Reconstructive & Aesthetic Surgery*

Received date: 22 October 2019
Accepted date: 1 March 2020

Please cite this article as: Miss. Michelle CI Lo , Dr. Jennifer Garioch , Professor Marc DS Moncrieff , Sequencing in management of in-transit melanoma metastasis: Diphencyprone versus isolate limb infusion, *Journal of Plastic, Reconstructive & Aesthetic Surgery* (2020), doi: https://doi.org/10.1016/j.bjps.2020.03.007

Sequencing in management of in-transit melanoma metastasis: Diphencyprone versus isolate limb infusion

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Abstract

Background In-transit metastases (ITMs) in melanoma are associated with poor prognosis, however a significant proportion of these patients survive for extended periods without further disease progression. We routinely use locoregional treatment e.g. Diphencyprone (DPCP) and/or isolated limb infusion (ILI) as long-term palliation. This study aimed to identify correct sequencing of these therapies based on disease burden and progression.

Method Retrospective evaluation of all melanoma patients with ITMs treated with DPCP/ILI/both from 2010-2017 at our Cancer Centre was performed. Patients were initially assessed in a multidisciplinary setting and empirically prescribed DPCP for low-disease burden, ILI for high-disease burden. Patient demographics, tumour characteristics, response to therapy, ITM progression and patient outcomes were analysed.

Results 78 patients (M:F=30:48), aged 47-95years (median 74years) treated with DPCP/ILI/both (n=44/21/13) were identified. Progression-free survival (PFS) was significantly increased in patients responsive to DPCP or ILI as initial treatment. Patients who failed on DPCP and subsequently treated with ILI had a significantly increased PFS compared to DPCP alone (p=0.026,HR=0.048). This was not the case with patients who were treated with DPCP following failed ILI. All patients who failed to respond to the initial therapy progressed within 6 months.

Conclusion Our study shows that careful stratification ITM patients according to disease burden is fundamental to optimal outcomes. High-disease burden patients benefit from initial ILI; low-disease burden patients should commence on DPCP. ILI can be considered in DPCP patients who fail early. Systemic therapy should be considered when locoregional therapies fail after 12 months or after rapid relapse following ILI.

Introduction

According to the 8th edition of the AJCC Melanoma Staging System, in-transit disease is defined as regional spread of tumour via lymphatic vessels in the dermis or subcutaneous tissue outside of nodal basins; in-transit metastases (ITMs) are included in stages IIIC and IIID and are considered locally advanced disease, associated with a 69% and 32% melanoma-specific survival rate respectively[1]. ITMs occur in up to 12% of all melanoma patients[2-5]. Within this cohort the disease volume, burden and progression can be diverse and variable. Currently there is no consensus on the optimal treatment protocol for ITMs. Multiple therapeutic modalities exist for the management of ITMs with the aim of producing locoregional control (palliation) of the disease. In our quaternary referral cancer centre we routinely use topical diphencyprone (DPCP) and isolated limb infusion (ILI) as our two locoregional treatment options for ITMs as alternatives to systemic therapy in carefully selected patients.

The exact mechanisms of actions of DPCP, a topical immunotherapy agent, in melanoma is unknown; it is a potent contact sensitizer that induces contact hypersensitivity reactions. The induced cytokines are IL-24 and IL-9, which are known to suppress melanoma activity[7]. We have previously described our experience with DPCP for the management of low-disease burden ITMs[7], where a response rate of 84% was demonstrated. There are several advantages to DPCP, including the ability for the patient to self-administer the treatment over large areas of the affected skin and it is relatively well-tolerated[8]. ILI is a minimally invasive, closed circuit technique that delivers concentrated doses of cytotoxic drugs (mephalan usually combined with actinomycin D) to the affected limb to achieve disease control[9,10]. Whilst, good locoregional control rates (overall response rate of 60-80%) have been described by multiple centres[11-13], the palliation comes at a cost of significant limb toxicity for some, which can significantly prolong the patient's rehabilitation.

With multiple modalities for treatment of ITMs; stratifying the appropriate treatment option is a challenge to the modern specialist skin multidisciplinary team (SSMDT). The complexity of this stratification is increased when the disease fails to respond to, becomes resistant to, or progresses on a given treatment. It is clear from multiple studies of both ILI and DPCP[13,14] that locoregional disease progression is associated with a poor prognosis in terms of overall survival. However, it is most commonly observed[14] that the patients' first site of relapse is locoregionally with no evidence of distant disease. Given the separate mechanism of action, it is unclear whether further locoregional treatments should be employed rather than proceeding to systemic therapy, particularly if the overall disease burden remains low. Accordingly, the aim of this study was to identify the correct sequencing of these therapies based on disease burden and progression.

Methods

A retrospective evaluation of all melanoma patients with ITMs treated with DPCP, ILI or both from 2010 to 2017 at the Norfolk & Norwich Skin Tumour Unit, a tertiary/quaternary melanoma service was performed. Within the context of a SSMDT, this cohort of patients were initially assessed and empirically prescribed DPCP for low disease burden and ILI for high disease burden as directed by the senior clinicians after clinical review in the multidisciplinary tertiary referral clinic (senior authors MM, JG). The treatment protocol for DPCP has been described by the senior authors[7]. Our protocol for performing ILI is nationally standardised and is very similar to that described by Professor Thompson's team at MIA[10,13]. Patients were followed up at 6-12 week intervals following the initiation of treatment by the clinician in the MDT clinic, where the patients' response to treatment was observed and recorded. In patients who failed their initial treatment and prior to consideration for commencing systemic therapy, the counterpart therapy was considered, i.e. patients who fail to respond to DPCP were considered for ILI and those who failed on ILI were treated with DPCP.

For the purposes of analysis, data regarding patient demographics, histopathological features of the primary melanoma, sequence of and response to therapy or therapies, ITM progression and patient outcomes were collected from a prospective institutional melanoma database. Kaplan-Meier probability estimate curves were generated to assess melanoma-specific (MSS) and progression-free survival (PFS).

Results

78 melanoma patients with ITMs treated with DPCP, ILI or both (n=44, 21, 13 respectively) were identified. 1 patient in the ILI-only cohort and 2 patients in the DPCP + ILI therapy cohort underwent ILI twice. Male to female ratio was 30:48; age ranged from 47 to 95 years (median 74 years). Primary melanoma distribution was limited to the limbs for ILI treatment as predicted; however, DPCP therapy was offered to patients who had head and neck or truncal melanomas and associated ITMs (Table 1).

Median PFS in the ILI-only group was 18 months, compared to 6 months in the DPCP-only group (p=0.22, not significant (NS)). Melanoma specific survival (MSS) was significantly increased in patients who demonstrated a response to either DPCP or ILI as the initial treatment compared to the dual therapy cohort, where median MSS was 32 months on DPCP, 69 months on ILI and 39 months on dual therapy respectively (p=0.01, Figure 1).

Patients who failed to respond to DPCP and were subsequently treated with ILI had a significantly increased PFS compared to DPCP alone (DPCP-only 8 months vs DPCP+ILI 20 months) (p=0.026, HR=0.47, Figure 2). This was not the case with patients who were treated with DPCP following failed ILI where PFS was 69 months in the ILI-only group compared to 38.5 months in the ILI+DPCP group (p=0.36, NS).

In all categories, we noted that patients who failed to respond to the initial therapy progressed within 6 months.

Discussion

Treatment for ITMs is not standardized i.e. there is no set sequencing of therapy or treatment strategy for this cohort of patients. NICE guidance for treating ITMs is palliative surgery in the first instance; however, in patients where surgery is not appropriate, a selection of treatment options ranging from systemic therapy, regional chemotherapy and local agents are recommended[15]. The aim of these is to gain locoregional control of the disease to allow long-term palliation of these patients. However, there is currently very little data available in comparing outcomes between non-surgical interventions.

In an MIA study, median survival following complete response from ILI for treatment of ITMs was 53 months[10], similar to our data where MSS was 69 months. Similarly, Read et al.

demonstrated that median overall survival from DPCP treatment commencement was 20.9 months and a disease-free survival of 12.3 months, comparable to our data[14].

ILI following failed DPCP improves MSS. Our data is seeming to suggest that ILI not only has a direct effect on ITMs as regional chemotherapy but is partly immune mediated.

Disease burden for ITMs was not definitively described in our study. PET-CTs and medical photography were used within a multidisciplinary setting to determine whether a patient was deemed to have low- or high-disease burden of ITMs; this, in turn, outlined their initial treatment strategy. Defining standardized ITM disease burden categories will further improve selecting appropriate management for this cohort of patients.

Our study shows that careful stratification ITM patients according to disease burden is fundamental to optimal patient outcomes. Those with high-disease burden benefit from initial ILI, whereas those with low-disease burden can be trialled with DPCP. ILI can be considered in DPCP patients who fail early. Systemic therapy should be considered when locoregional therapies fail after 6 months or after rapid relapse following ILI. We suggest that treatment priority should be based on volume and site of disease. We propose the following algorithm (Figure 3) on managing patients with ITMs.

Conclusion

Our data suggests that DPCP and ILI both have roles in managing ITMs by offering prolonged locoregional disease control, and reserving systemic therapies for disease progression. However, disease burden is an important consideration when basing initial treatment strategies. Comparatives studies is merited to more precisely evaluate individual non-surgical treatment options for managing ITMs in melanoma, including combinations of such treatments.

Funding: none

Conflict of Interest: none

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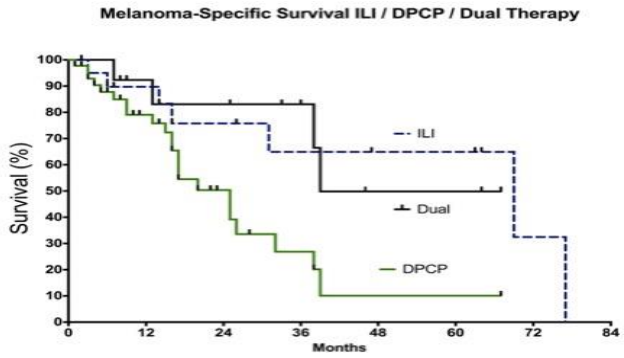

Figure 1: Melanoma-specific survival comparing patients undergoing ILI-only, DPCP-only and dual therapy treatment for in-transit melanoma

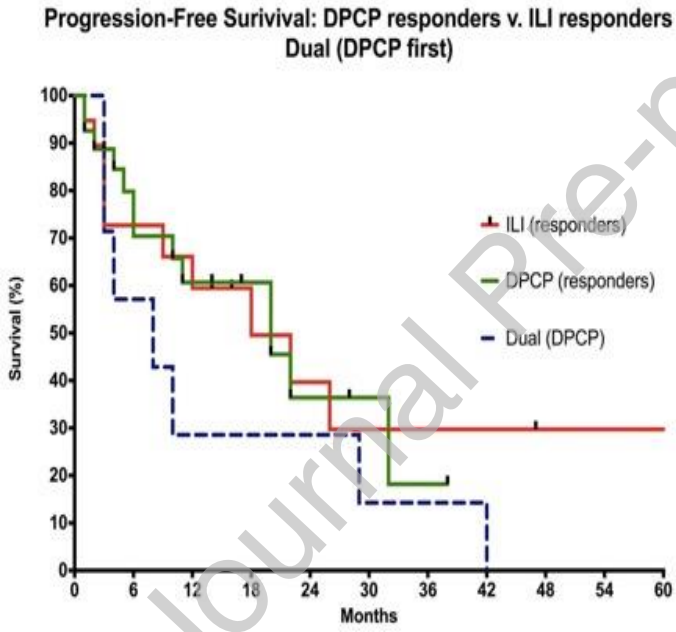

Figure 2. PFS in patients who respond to first line DPCP vs first line ILI and those who were treated with dual therapy (DPCP first).

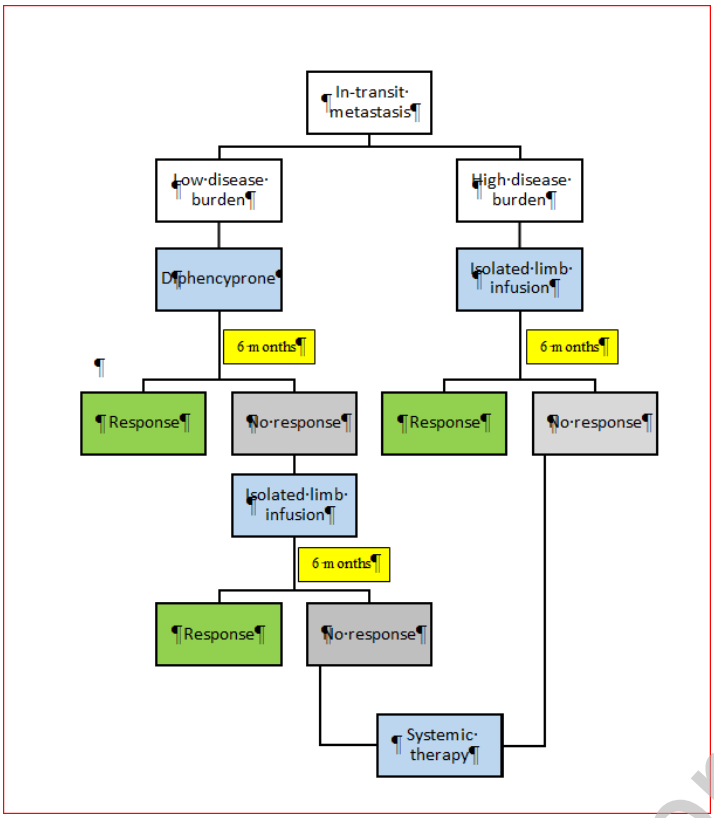

Figure 3. Proposed sequencing algorithm on managing patients with in-transit metastasis using Diphencyprone, isolated limb infusion and systemic therapy.

Table 1: patient demographics and primary melanoma characteristics (N/A: not applicable)

	DPCP only	**ILI only**	**DPCP and ILI**
Number of patients (n)	44	21	13
Median age (years)	77	70	75
Primary melanoma distribution			
Head and neck	8	N/A	N/A
Trunk	7	N/A	N/A
Upper limb	5	1	0
Lower limb	24	18	13
Unknown primary	0	2	0
Median Breslow thickness	2.5	2.65	2.5

(mm)			
Ulceration			
Yes	19	6	6
No	23	8	2
Unknown	2	7	5