Co-immunotherapy with interleukin-2 and taurolidine for progressive metastatic melanoma

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ABSTRACT

Background Recombinant interleukin-2(rIL-2) therapy in metastatic melanoma is limited by toxicities, particularly vascular leak syndrome(VLS). Taurolidine potentiates the anti-neoplastic effects of IL-2 while reducing its associated endothelial cell dysfunction in experimental settings. We hypothesized that co-administration of rIL-2 with taurolidine could enhance tolerability without weakening effectiveness.

Methods Eleven patients with progressive metastatic melanoma received high-dose rIL-2 with co-infusion of taurolidine. Patients were monitored for the development of toxicities and evidence of response.

Results Ten patients tolerated twenty-nine courses of high-dose rIL-2 without dose-reduction. Most toxicities were low-grade. No patient developed VLS. Seven patients died from disease progression. Two had complete clinical and radiological responses to treatment. Two patients remain alive despite evidence of disease progression a mean of 17.5 months after diagnosing metastatic disease.

Conclusion Co-administration of taurolidine with high-dose rIL-2 in stage IV melanoma patients appears to greatly enhance the tolerability of this regime without diminishing its therapeutic value.

INTRODUCTION

The prognosis for patients with metastatic melanoma remains dismal, with a median survival time after diagnosis of five to eight months.[1] Treatment of stage IV disease with recombinant interleukin 2 (rIL-2) represents one of the earliest attempts at systemic immunomodulation as a therapy for cancer.[2] However, overall response rates have been lower than originally anticipated as administration of high-dose IL-2 is limited by severe dose-related toxicity. While this toxicity can manifest in multiple organ systems, the most common serious complication is vascular leak syndrome (VLS) resulting in hypovolaemic shock and acute respiratory distress syndrome (ARDS) that leads to the need for inotropic support and pulmonary intubation in up to 80% and 12% of cases respectively.[3] Unfortunately, the co-administration of agents intended to ameliorate these toxicities have tended to impact negatively on the anti-neoplastic effects of the immunotherapy resulting in a net reduction in its therapeutic index.[4]

While much research has focused on developing agents that may augment the anti-cancer effects of lower-dose IL-2,[5,6,7,8] to date, relatively little evidence exists regarding the use of biologic response modifiers of the immune system that could selectively alter the balance between the two fundamental effects of IL-2 (i.e. augmentation of lymphokine activated killer (LAK) cell tumour cytotoxicity whilst simultaneously reducing the associated endothelial cell injury). Taurolidine, a derivative of the amino acid taurine, has been shown to attenuate rIL-2-activated, LAK cell-mediated endothelial cell dysfunction and lysis and is known to inhibit melanoma tumour cell growth both in-vitro and in-vivo.[9,10,11,12] We hypothesized therefore that the co-administration of rIL-2 and taurolidine to patients with stage IV melanoma could attenuate the toxicity of high-dose rIL-2 infusion without compromising its therapeutic index.

PATIENTS AND METHODS

Eleven patients (7 males) with advanced and progressive metastatic melanoma were enrolled in a phase III clinical study after obtaining approval from both the Irish Medicines Board and our local Ethics committee as well as full-informed individual consent. The mean age (range) of the patients was

Table 1
DECRESCENDO DOSE REGIMEN OF IL-2 AND TAUROLIDINE FOR PATIENTS WITH STAGE IV MELANOMA (MIU/M2 = MILLION INTERNATIONAL UNITS PER METRE SQUARED)

INTERLEUKIN-2	Decrescendo regimen of 72 miu/m^2 over 120 hours
Day One	18 miu m^{-2} IL-2 infusion over the first 8 hours
	18 miu m^{-2} IL-2 infusion over the next 16 hours
Day Two	18 miu m^{-2} IL-2 infusion over 24 hours
Day Three to Five	18 miu m^{-2} IL-2 infusion over 72 hours.
TAUROLIDINE	Taurolidine 2% w/v (250mls/12 hours) via continuous infusion

50 (23-63) years. The locations of the primary lesions were upper limb (n=4), lower limb (n=3), head and neck (n=2) and trunk (n=1) with one patient having an unknown primary site (despite extensive investigation). The mean Breslow's thickness was 4.8 mm (range 0.8mm to 16mm). The metastatic load of each patient was significant and was multifocal in five patients. Metastatic sites included the lung (n=5), liver (n=5), supraclavicular fossa (n=3), bone (n=1), kidney (n=1), bowel (n=1) and subcutaneous tissues (n=2). All patients had progressive disease despite having previously undergone appropriate surgical management (resection of the primary lesion and regional lymphadenectomy). Six of these patients had also received adjuvant treatment because of the poor prognosis portended by their primary lesions. Five had had immunotherapy (interferon-α) while four had received chemotherapy (DTIC) (Table 2).

In an approved protocol, 72 miu/m^2 rIL-2 was administered via a central venous catheter to the patients in a decrescendo regimen over 120 hours (Table 1). Simultaneously, the patients received a continuous infusion of 2% w/v taurolidine (bis (1,1dioxoperhydro-1,2,4-thiabiazin-4-yl)methane, Geistlich Pharma). Patients were scheduled for four courses of treatment in total with each course being separated by a three-week break. Disease restaging by whole body CT scan was performed after two and four treatments or as clinically indicated. During treatment, patients had their blood pressure and pulse recorded every 30 minutes for the first three hours and hourly thereafter for the duration of treatment. Urine output was measured hourly. Haematological and biochemical laboratory indices were checked daily as were body weights. Chest auscultation was performed twice daily and a chest radiograph performed before treatment began and repeated subsequently depending on clinical course.

RESULTS

Cumulatively, the patients received 30 courses of the co-infusion regime. Ten patients tolerated 29 courses of high-dose rIL-2 and taurolidine without dose reduction or treatment cessation. The majority of toxicities were low-grade with flushing and nausea being the most common adverse events. No patient developed significant hypotension or ARDS (and therefore none required intensive care admission for vasopressor therapy or pulmonary intubation). One patient developed acute renal failure requiring cessation of treatment, whereupon his renal function returned to its baseline level. No patient developed catheter-associated sepsis.

Seven patients died from further progression of their disease early in their treatment course. Two patients had complete clinical and radiological responses following three and five treatment courses with no evidence of disease at 8 and 55 months respectively. The two other patients have survived for 8 and 27 months respectively despite radiological evidence of disease progression (Table 2).

DISCUSSION

Stage IV melanoma is refractory to most standard systemic therapy and so is associated with a dismal prognosis. The objective response rate to dacarbazine (DTIC) and the nitrosoureas, carmustine (BCNU) and lomustine (CCNU), is approximately 10% to 20% and such responses are usually short-lived (ranging from 3 to 6 months).[13] While aggressive surgical resection policies may be pursued for some patients with isolated metastatic disease,[14] evidence of progressive metastases should dissuade from its use. Furthermore, as the majority of post-surgical metastatic patients eventually relapse and succumb to distant disease,[15] the development of effective systemic therapies remains a crucial aspect of improving survival in patients with advanced disease. Although active immunotherapies (i.e. anti-

Table 2 (a)
PATIENT DEMOGRAPHICS & TREATMENTS

PATIENT	AGE	SITE OF PRIMARY MELANOMA	DEPTH OF PRIMARY MELANOMA (MM)	PRIMARY SURGERY	NODAL STATUS	ADJUVANT THERAPIES
1	48	Trunk	16	WLE & Radical Neck Dissection	Positive	Interferon
2	50	Upper Limb	5.5	WLE & Axillary Clearance	Positive	Interferon/DTIC
3	61	Lower Limb	1	WLE & SLNB	Negative	
4	23	Upper Limb	1.4	WLE & SLNB	Negative	DTIC
5	50	Scalp	0.8	WLE & Grafting		
6	45	Upper Limb	3.8	WLE & SLNB	Negative	Interferon/DTIC
7	60	Upper Limb	2.2	WLE & SLNB	Negative	Interferon/DTIC
8	59	Unknown 10	Unknown	Axillary Clearance & WLE	Positive	
9	58	Lower Limb	7	WLE & SLNB	Negative	
10	63	Eye	Ocular	Enucleation		
11	33	Lower Limb	5.5	Toe amputation & Groin Dissection	Negative	Interferon

Table 2 (b)
PATIENT DEMOGRAPHICS & TREATMENTS

PT.	TIME TO DIAGNOSING METASTASES (MONTHS)	SITE OF METASTASES	SECONDARY SURGERY	NO OF CYCLES IL2 & TAUROLIDINE	TOXICITIES	STATUS	SURVIVAL (MONTHS)
1	16	Supraclavicular Fossa		5	Nausea, Flushing	N.E.D.	55
2	20	Supraclavicular Fossa		5	Nausea, Fatigue	R.I.P.	41
3	48	Lung / Bone / Cutaneous	WLE	4	Fatigue, Diarrhoea	Disease Progression	27
4	60	Liver / Lung		3	Nausea	Disease Progression	8
5	96	Gut / Lung / Kidney	Bowel Resection	3	Nausea, Flushing	N.E.D.	8
6	23	Liver / Lung		2	Nausea, Flushing	R.I.P.	10
7	17	Axillary / Liver	Axillary Clearance	1		R.I.P.	9
8	Metastases at presentation	Subcutaneous / Supraclavicular Fossa / Axilla		2		R.I.P.	6
9	10	Lung / Groin	Groin Clearance	1	Acute Renal Failure	R.I.P.	3
10	Metastases at presentation	Liver		1		R.I.P.	2
11	4	Liver		3		R.I.P.	11

melanoma vaccine-based regimens) hold much promise, no such therapies have yet obtained FDA-approval and so are not in widespread use. Therefore, adoptive immunotherapy strategies are currently of most potential benefit to high-risk patients.[16]

The use of IL-2 as a single immunotherapeutic agent, although associated with improved disease response rates and survival,[17] has been significantly hampered by its toxicity. IL-2 toxicity can manifest in multiple organ systems, most significantly in the heart, lungs, kidneys and central nervous system. The most common manifestation of IL-2 toxicity is vascular leak syndrome, resulting in a hypovolaemic state and fluid accumulation in the extravascular space. The potential for the development of vascular leak syndrome as the most significant adverse effect has in the past mandated that patients undergoing this treatment be monitored in an intensive care setting to facilitate the early recognition and management of the clinical sequelae of ARDS and hypotension, often requiring inotropic support. Furthermore, development of this toxicity frequently leads to dose reduction or even treatment cessation undermining its potential to achieve disease stability or regression. In this cohort, no patient required admission to the intensive care unit or inotropic support despite receiving high-dose IL-2 infusion.

Taurolidine is a stable analogue of the non-essential amino acid taurine. This agent has previously been shown to markedly reduce IL-2-mediated endothelial cell dysfunction and lung injury,[9,18] acting perhaps by its effects on intracellular calcium flux as well as its ability to regulate lymphocyte activation and cytolysis.[19,20] Furthermore, unlike other agents given to attenuate the toxicity associated with IL-2,[4] taurine derivatives actually potentiate the therapeutic index of IL-2 immunotherapy in animal melanoma models by augmenting IL-2 induction of LAK activity in addition to exerting IL-2-independent anti-neoplastic effects.[21] Although this study comprises a novel indication for taurolidine in humans, its safety in the doses given has been well documented previously in a variety of settings.[22,23,24]

While this study was not designed to test for an augmentation in the efficacy of IL-2, our finding that two of the patients with late, progressive disease that was resistant to other strategies had complete clinical and radiological responses suggests that this may be the case. Furthermore, the attenuation of significant toxicity with co-administration of taurolidine suggests the potential for either IL-2 dose increment or regime prolongation in order to further improve outcome of patients with late stage melanoma. Interestingly, in this study, no patient developed catheter-associated line sepsis although this has previously been reported to complicate IL-2 treatment in 4-18% of patients.[3] Taurolidine has been previously reported to reduce the incidence of bacteraemia / septicaemia in patients with long-term indwelling central venous access catheters.[25] This suggests an additional beneficial effect of the strategy that is worthy of further scrutiny.

In conclusion, we believe that the excellent toleration of the therapeutic strategy described in this small number of patients warrants further scrutiny in the form of a randomized clinical trial in patients with poor-outcome metastatic melanoma.

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