Grade 4 Thrombocytopenia During Treatment with High-Dose IL-2 (HD IL-2) is a Predictor of Response in Melanoma but Not in Renal Cell Cancer.

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Introduction

- High dose IL-2 is the only therapy demonstrated to provide long term remission in Melanoma and Renal Cell Cancer.
- Responses are seen in a minority of patients but can be durable.
- Significant toxicity and high cost.

Introduction

- We observed severe thrombocytopenia in patients with melanoma who responded to IL-2.

- Prompted us to ask the question: does severe thrombocytopenia predict response to IL-2 in our patient population?

Introduction

- Multiple reviews evaluating predictors of response to IL-2.
- Most published data generated from patients treated at the NCI between 1985 and 1999.

Patient Characteristics	Treatment Parameters
Site of Disease	Rebound Lymphocytosis
Performance Status	Vitiligo in Melanoma
	Hypothyroidism

Introduction

- Reviews that have looked at change in platelet counts have had mixed results.

- Two studies demonstrated possible correlation.
  - Phan GQ, et al. J Clin Oncol. 2001;19:3477.
    - Platelet nadir lower in responders, $p = 0.053$.
  - Royal RE, et al. Cancer J Sci Am. 1996;2:91
    - Lower platelet nadir in responders with $p = 0.004$ in RCC and $p = 0.08$ in melanoma patients.

- Other authors looked for but did not find correlation.
  - Rosenberg SA, et al. Ann Surg. 1998;228:307.
  - MacFarlane MP, et al. Cancer. 1995;75:1030.

Study Patients

- 44 patients with metastatic melanoma or renal cell cancer treated at Duke University Medical Center between October of 2002 and August of 2004.
- Treated with standard intravenous bolus high dose IL-2 regimen:
  - 600,000 IU/kg every 8 hours for up to 14 doses during weeks 1 and 3 of 12 week course.
- Response and progression defined by RECIST criteria.

Patient Characteristics (N =44)

	Number	(%)
Disease		
Renal Cell Cancer	19	(43)
Melanoma	25	(57)
Sex		
Male	32	(73)
Female	12	(27)
Age		
Mean	52	
Range	24 to 72	
Number of Sites of Metastasis		
Mean	2	
Range	1 to 5	
ECOG		
0	38	(86)
1	6	(14)
Prior Therapy		
Adjuvant Therapy	2	(5)
Chemotherapy or Biochemotherapy	5	(11)
Radiotherapy	2	(5)
Stage - Melanoma		
M1a	6	(24)
M1b or M1c	19	(76)

Patient Characteristics Versus Response

	Patients	Responders (%)	p value
Disease			
Renal Cell Cancer	19	5 (26)	0.9
Melanoma	25	7 (26)	
Sex			
Male	32	7 (22)	0.19
Female	12	5 (42)	
ECOG			
0	38	12 (32)	0.11
1	6	0 (0)	
Prior Therapy			
None	38	9 (24)	0.18
Chemotherapy or Biochemotherapy	5	3 (60)	
Radiotherapy	2	0 (0)	
Stage - Melanoma			
M1a	6	3 (50)	0.169
M1b or M1c	19	4 (21)	

	Outcome	Mean	
Age	R *	57	0.15
	NR	51	
Number of Sites of Metastasis	R	1.5	0.11
	NR	2.1	

* R = Responders
NR = Non Responders

Treatment Parameters Versus Response
All Patients (N=44)

	Outcome	Mean	p value
Number of Doses in Cycle # 1	R *	22.7	0.12
	NR	20.6	
Peak Lymphocyte Count, Week 1	R	4931	0.9
	NR	4214	
Fold Change in Lymphocytes, Week 1	R	3	0.98
	NR	2.8	
Platelet Nadir, Week 1	R	47	0.0741
	NR	70	
Fold Decrease in Platelets, Week 1	R	8.9	0.0041
	NR	4.1	

* R = Responders
NR = Non Responders

Platelet Change in Melanoma versus Renal Cell Cancer

	Outcome	Mean	p value
Melanoma (N = 25)			
Fold Decrease in Platelets, Week 1	R*	12.4	0.004
	NR	4.4	
Platelet Nadir, Week 1	R	28	0.0047
	NR	67	
Renal Cell Cancer (N = 19)			
Fold Decrease in Platelets, Week 1	R	4.1	0.43
	NR	3.7	
Platelet Nadir, Week 1	R	73	1
	NR	73	

* R = Responders
NR = Non Responders

Response Rate and Grade of Thrombocytopenia in Melanoma

	Patients	Responders (%)	p value
Grade 4	5	5 (100)	< 0.0001
Grade 1 to 3	20	2 (10)	
Grade 3 & 4	11	6 (55)	0.009
Grade 1 & 2	14	1 (7)	

Multivariate Analysis

- Female sex correlated with response and change in platelet count.
- For patients with melanoma, accounting for number of doses, stage, age and sex, $p = 0.01$ for association between response and fold decrease in platelet count.
- c-index = 0.89, showing that change in platelet count was a strong predictor of response in our patients with melanoma.

Etiology of Correlation

- Why does thrombocytopenia correlate with response to HD IL-2 therapy in melanoma patients?

- Thrombocytopenia may be surrogate marker of non-specific immune activation.
  - Platelet consumption via microthrombosis.
  - Proinflammatory cytokine-induced activation of reticuloendothelial system.

Etiology of Correlation

- Platelet activation may play a direct role in antitumor response.
  - Through increased platelet aggregation.
    - Selective expression of endothelial adhesion molecules on tumor microvasculature.
    - Formation of microthrombi in tumor bed.
  - Release of CD40L by activated platelets
    - Activates plasmacytoid dendritic cells.
    - Facilitates B cell presentation of melanoma antigens.

Etiology of Correlation

- Thrombocytopenia may mark the development of a specific immune response.
  - Melanoma cells and platelets share key antigens.
    - glycoprotein IIb/IIIa
    - CD63
    - Vitronectin receptor $\alpha_v\beta_3$
  - IL-2 may induce production of antibodies to these antigens.
    - Transient ITP as an autoimmune phenomenon associated with response.
    - Antiplatelet antibodies cross-reactive with tumor

Conclusions

- Fold decrease in platelet count and grade 4 thrombocytopenia after week one of HD IL-2 is strong predictor of response for patients with melanoma in this sample.

- Further studies will be needed to determine mechanism of thrombocytopenia and its clinical relevance.