Clinical Trial of High-Dose Pegylated-Interferon-Alfa-2b Combined With Phototherapy in Advanced Stage Mycosis Fungoides

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The combination of Interferon-α-2b (IFN-α-2b) and phototherapy is highly effective in treating mycosis fungoides (MF) but side effects often lead to discontinuation of therapy.[1] The development of pegylated interferon-α-2b (PEG-IFN-α-2b), a modified interferon with a polyethylene glycol (PEG) chain with 10-fold longer plasma half-life in comparison to IFN-α-2b, showed better tolerability with fewer dose-limiting toxicities than conventional IFN-α-2b. A case report of PEG-IFN-α-2b successfully treating a patient with MF and hepatitis C prompted us to explore the combination of PEG-IFN-α-2b and phototherapy in MF.[2] Consistent with this hypothesis, Huesken et al demonstrated high response and increased survival in treatment group with PEG-IFN-α-2b (1.5 µg/kg weekly) plus psoralen with UVA (PUVA) versus IFN-α-2b (9 MIU 3×/week) plus PUVA.[3]

An open label pilot study was conducted between 2008–2011 in patients with advanced stage MF/SS (stage IIB-IVB) who had ECOG ≤1 and no previous interferon therapy. Five patients with MF [IIB (4/7), IIIB (1/7)] and 2 with Sézary Syndrome (SS) were enrolled with a median age of 58 years (range, 38–79) (Table1). They received PEG-IFN-α-2b at a starting dose of 1.5 µg/kg, administered subcutaneously once weekly with dose escalation up to 9 µg/kg or maximum tolerated dose. PUVA treatment or narrow-band UVB was scheduled three times weekly following the institutional standard protocol. Primary end point was to

TABLE 1.

Study Population Characteristics and Outcome. Maximum tolerated dose=MTD. Prior therapies included 1=topical steroids, 2=topical nitrogen mustard, 3=NB-UVB, 4a=local radiation therapy, 4b=total skin electron beam therapy, 5=alemtuzumab, 6=methotrexate (2 doses only), 7=topical calcipotriene/betamethasone, 8=cyclosporine, 9=systemic steroids

Case No.	Age	Gender	Race	Prior Therapy	Stage	Pathology Diagnosis	Photo-therapy	Best Response	PEG-IFN Treatment duration (weeks)	MTD (µg/kg)	Reason for Discontinuation	Progression Free Survival (months)	Outcome	Cause of Death	Overall Survival (months)
1	58	M	W	1	IVA (B2)	CTCL (MF vs. SS)	PUVA	PR	40	9	Progression	10	Dead	Disease	30
2	79	F	W	1, 2, 3, 4a	IIB (B0)	MF, LCT	PUVA	CR	10	4.5	Progression	3.5	Dead	Disease	46
3	78	M	W	1, 3, 4b, 5, 8	IVA (B2)	MF, LCT	PUVA	PR	22	6	Heart failure	6	Dead	Unrelated to disease	31
4	38	M	W	1, 4a	IIB (B0)	MF, LCT	PUVA	PR	2	1.5	Neutropenia, Progression	1.5	Dead	Disease	34
5	45	M	W	1, 4a	IIB (B0)	folliculotropic MF	PUVA	PR	35	3	Progression, Neutropenia	8.5	Alive	--	136
6	58	F	AA	3, 6, 9	IIB (B0)	folliculotropic MF, LCT	PUVA	SD	9	6	Progression	2.5	Dead	Disease	95
7	48	F	AA	1, 7	IIIB (B1)	MF, LCT	NB-UVB	SD	2	1.5	Progression, Infection	0.5	Dead	Disease	6

TABLE 2.

Encountered Side Effects During Treatment With PEG-IFN-α-2b		
Side effects	**Any grade**	**Grade III/IV**
Constitutional	100% (7/7)	14.3% (1/7)
Myelosuppression	100% (7/7)	--
Lymphopenia	71.4% (5/7)	--
Neutropenia	71.4% (5/7)	14.3% (1/7)
Anemia	57.1% (4/7)	--
Thrombocytopenia	43.6% (3/7)	
Metabolic/laboratory abnormalities	85.7 % (6/7)	--
Gastrointestinal	28.6% (2/7)	--
Pain	43.6% (3/7)	14.3% (1/7)
Musculoskeletal	14.3% (1/7)	--
Dermatologic	71.4% (5/7)	--
Infection	14.3% (1/7)	--
Cardiac	14.3% (1/7)	14.3% (1/7)

determine dose limiting toxicities of Peg-IFN-α-2b. Secondary end points were the number of patients exhibiting complete remission (CR) and duration of response. Response was assessed according to the Composite Assessment of Index Lesion Disease Severity (CAILS). During dose escalation phase patients were monitored for side effects every other week and in maintenance phase response was assessed every 4 weeks. The median duration of weekly PEG-IFN-α-2b injections received was 10 weeks (2–40 weeks) with an average dose of 3.76 µg/kg. Median phototherapy duration was 12 weeks (2–48 weeks).

While 5/7 patients met criteria for response including one with CR, the median progression free survival was 3.5 months (0.5–10.0 months; Table1). Early termination of study protocol occurred in all cases and reasons were disease progression (2/7), side effects (1/7), or both (3/7) (Table1). All patients had constitutional symptoms and hematologic abnormalities (Table 2). With a median follow up of 34 months (5–135 months), 6/7 patients died, with 5/6 attributed to disease. The only patient (case 5) still alive (>10–year survival) is currently undergoing treatment for transformed MF IVB.

This study was designed as a feasibility trial with intra-patient dose escalation permitted. Efficacy estimates are limited by the sample size and treatment interruptions due to PEG-IFN-α-2b side effects. All patients experienced side effects, which resulted in either treatment interruption or complete discontinuation and we therefore conclude that the administered PEG-IFN-α-2b dose was too high. Today PEG-IFN-α-2b is dosed at 1.5 µg/kg and has been shown to be most effective and safe.[4] However, during the time the study was conducted, it was common practice to increase unpegylated interferon dose as permitted by side effects.[5] Still, the short duration of response suggests that high dose PEG-IFN-α-2b and phototherapy may not be considered a viable treatment option for advanced stages of MF/SS, especially with large cell transformation, at least in our study.[1]

In conclusion, in this small clinical trial with advanced stage MF/SS, five of seven patients showed response to high dose pegylated interferon in combination with phototherapy with the most common reason for discontinuation being hematologic toxicity and disease progression. Lower doses of pegylated IFN with phototherapy is likely to be a more efficacious and tolerable strategy.[5] Nevertheless, interferons in combination with phototherapy are indispensable therapeutics in the treatment of MF and therefore Merck's recent announcement of future discontinuation of IFN-α-2b and PEG-IFN-α-2b poses a serious challenge to the treatment of CTCL.

DISCLOSURES

The authors have no conflict of interest to declare.

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