Use of Mesenchymal Stem Cells (Prochymal™) to Treat Pediatric Patients with Severe (Grade III-IV) acute Graft Versus Host Disease Refractory to Steroid and Other Agents

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Data was presented at the December 2007 American Society of Hematology meeting

Protocol/Methods

Background

Severe acute Graft versus Host Disease (aGvHD) that fails to respond to steroids and other immunosuppressive agents is associated with 180 day survival of less than 20%. Preliminary studies have shown that human mesenchymal stem cells (hMSCs, Prochymal™, Osiris Therapeutics, Inc.) have immunomodulatory and tissue regenerative properties. This report summarizes the safety and efficacy of Prochymal for the compassionate treatment of severe (Grades III/IV) acute GvHD in pediatric patients who failed steroids and multiple 2nd line immunosuppressive therapies.

Patients

- 12 pediatric patients with severe aGvHD (Grade III, n=6 and IV, n=6) were treated from July 2005 to July 2007
- To be eligible for compassionate use, patients must have exhausted all reasonable therapeutic alternatives
- Patients had failed an average of 3.2 lines of therapy prior to treatment with Prochymal
- Patients suffered with aGvHD for a median of 30 days (16-181days) prior to initiation of Prochymal therapy
- Patients from 5 different centers were enrolled
- Median patient age was 6 years (range 0.4-15 years)
- Each treatment plan received IRB and FDA approval

Prochymal Therapy

Treatment Plan:

Infusion: Cells were given IV over 1 hour for patients under 35kg and at a rate of 4-6mL/min for patients ≥35kg. Patients received hydrocortisone and diphenylhydramine 30 minutes prior to infusion of Prochymal.

Induction therapy: 2 x 10^6 MSC/kg/infusion, twice a week for 4 weeks. Patients #'s 1 and 2 received 8 x 10^6 MSC/kg/infusion under a different treatment plan (see Table).

Maintenance therapy: Option for additional infusions of 2 x 10^6 MSC/kg/infusion, once a week for the subsequent 4 weeks. Therapy was provided to patients who did not achieve a CR during the induction therapy.

Prochymal™ *(ex vivo cultured human mesenchymal stem cells)*
The product was manufactured by Osiris and consists of a population of homogeneous MSCs characterized by cell surface phenotype. hMSCs are isolated from an unrelated, unmatched donor-derived BM aspirate after donor screening and testing according to FDA requirements. The cells are expanded in culture to permit up to 5,000 doses to be obtained from a single donation. The hMSCs are tested for potential pathogens, mycoplasma, sterility, endotoxins and potency. The cells are formulated in Plasmalyte A containing 5% human serum albumin and 10% DMSO and aseptically packaged into Cryocyte bags.

Preparation. Cells were thawed and resuspended in Plasmalyte A. The final product had a cell concentration of 2.5 x 10^6 MSC/mL and a DMSO concentration of 3.75%. All products had a cell viability ≥70%. The volume administered was dependent upon body weight.

Patient Transplantation History

No	Gender	Age	Disease	Conditioning	Stem cells	Donor/match
1	Male	5m	ALD	Red Int	BM+UCB	RD 6/6
2	Male	8m	M Osteopet	Red Int	UCB	UD 4/6
3	Male	6y	HLH	Ablative	BM	UD 10/10
4	Male	2y	Hurler's	Red Int	UCB	UD 4/6
5	Male	13y	APML	Red Int	UCB	UD 4/6
6	Male	2y	AML	Ablative	UCB	UD 5/6
7	Male	15y	HLH	Ablative	UCB+haplo-PBSC	UD 5/6
8	Male	4y	ALL	Ablative	PBSC	UD 9/10
9	Male	15y	AML	Red Int	UCB	UD 5/6
10	Female	2y	MPD/Eos	Ablative	UCB	UD 6/6
11	Female	6y	ANLL	Red Int	UCB	UD 4/6
12	Male	13y	ALL	Ablative	BM	UD 10/10

ALD: adrenoleukodystrophy; HLH: hemophagocytic lymphohistiocytosis; APML: acute promyelocytic leukemia; AML: acute myeloid leukemia; ALL: acute lymphocytic leukemia; MPD/eos: myeloproliferative disease/eosinophilia; ANLL: acute non-lymphocytic leukemia; Hurler's: Hurler's syndrome; M Osteopet: malignant osteopetrosis; Red Int: reduced intensity; BM: bone marrow; UCB: umbilical cord blood cells; PBSC:peripheral blood stem cells; haplo PBSC:CD34 selected cells; RD: related donor; UD: unrelated donor;

Patient GvHD History

No	Onset aGvHD Post Transplantation	aGvHD Before Prochymal	GvHD Severity at start of Prochymal Infusion	GvHD Therapies prior to Prochymal
	DAYS	DAYS	GRADE	(Number) Agent
1	70	20	IV	(4) Solumedrol, cellcept, infliximab daclizumab
2	81	45	III	(4) Solumedrol, daclizumab, cellcept, prograf
3	22	46	IV	(3) Solumedrol, infliximab, entanercept
4	98	119	III	(4) Solumedrol, daclizumab, infliximab, budesonide
5	56	181	IV	(2) Solmedrol, daclizumab
6	72	30	IV	(4) Solumedrol, cellcept, infliximab, OKT3
7	27	18	IV	(4) Solumedrol, Zenapax, cellcept, infliximab, rituxan
8	22	76	III	(3) Solmedrol, infliximab, ECP
9	84	19	III	(2) Solmedrol, budesonide
10	33	38	III	(2) Solumedrol, infliximab
11	93	125	III	(3) Solmedrol, daclizumab, cellcept
12	80	157	IV	(3) Solumedrol, daclizumab, cellcept

GvHD Severity and Prochymal Treatment Plan

No	GI/Skin/Liver (stages)	Grade GvHD	No. Infusions	hMSC/kg /Infusion	Treatment Plan
1	4/1/3	IV	21[a]	8 x 10^6; 2 x 10^6	2/wk for 4 wk; 1/wk 13 wk
2	3/3/0	III	2	8 x 10^6	Day 1 & 4
3	4/2/0	IV	12	2 x 10^6	2/wk for 4 wk; 1/wk for 4 wk
4	3/0/0	III	12	2 x 10^6	2/wk for 4 wk; 1/wk for 4 wk
5	4/0/2	IV	9	2 x 10^6	2/wk for 4 wk; 1/wk for 4 wk
6	4/0/0	IV	8	2 x 10^6	2/wk for 4 wk
7	4/1/3	IV	12	2 x 10^6	2/wk for 4 wk; 1/wk for 4 wk
8	4/1/0	IV	7	2 x 10^6	2/wk for 4 wk
9	3/0/0	III	8	2 x 10^6	2/wk for 4 wk
10	3/0/0	III	3[b]	2 x 10^6	2/wk for 4 wk
11	3/0/0	III	8	2 x 10^6	2/wk for 4 wk
12	4/0/1	IV	12+8[c]	2 x 10^6	2/wk for 4 wk; 1/wk for 4 wk; 2/wk for 4 wk

[a] 11 infusions were administered at 8 x 10^6 hMSC/kg and 10 infusions were administered at 2 x 10^6 hMSC/kg
[b] Patient was discontinued at parents' request
[c] Patient was continued on therapy to allow for removal of steroids

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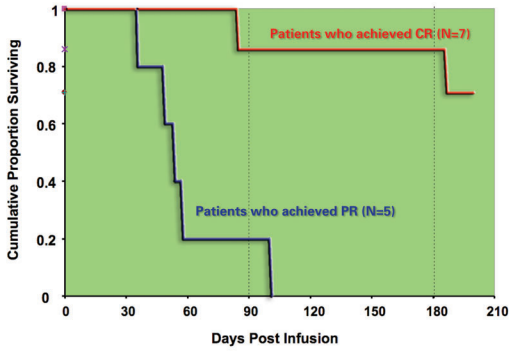
Results

GvHD Response

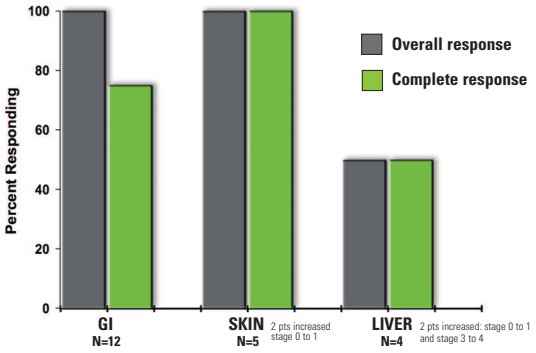
All patients responded to Prochymal therapy; 7 (58%) patients achieved a CR

	Prior to Prochymal Treatment		After Completion of Prochymal Treatment		Response
No	GI/Skin/Liver (stages)	Grade	GI/Skin/Liver (stages)	Grade	
1	4/1/3	IV	0/0/4	IV	PR
2	3/3/0	III	0/0/0	0	CR
3	4/2/0	IV	0/0/0	0	CR
4	3/0/0	III	0/0/0	0	CR
5	4/0/2	IV	3/1/2	III	PR
6	4/0/0	IV	0/0/0	0	CR
7	4/1/3	IV	0/0/0	0	CR
8	4/1/0	IV	0/0/0	0	CR
9	3/0/0	III	1/0/0	I	PR
10	3/0/0	III	2/0/0	II	PR
11	3/0/0	III	0/1/1	II	PR
12	4/0/1	IV	0/0/0	0	CR

Survival and Response



Response by Organ System



Current Status

- All patients tolerated treatment and there were no SAEs related to the administration of Prochymal
- 100 day survival (*from initiation of Prochymal*) is 58% (7/12)
- By publication (median follow up 229 days), 7 patients had died
- Patient survival and response status

Part #	Death post 1st infusion DAY	Response	Cause
7*	85	CR	Multiorgan failure, fungal infection
3	185	CR	Sepsis
5	36	PR	CMV encephalitis
11	49	PR	Respiratory failure, fungal infection
10	54	PR	EBV LPD
9	58	PR	Multiorgan failure, EBV LPD
1	101	PR	Sepsis, candida

* Patient received a liver transplantation for severe hepatitis on day 19 after starting induction therapy.

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Summary/Conclusion

Summary

- **All patients achieved a clinical response in at least one organ system after Prochymal infusions**
- **58% (7/12) of the patients achieved a complete response at the end of Prochymal therapy**
- **Best responses were seen in patients with severe (stages 3/4) GI GvHD:**
  - 75% (9/12) achieved a complete resolution of GI symptoms
- **42% (5/12) of the patients are alive with a median follow up of 229 days**
- **All surviving patients had achieved a complete response**
- **The infusion of Prochymal was safe and well tolerated. No infusional toxicities were observed**

Conclusions

- **The administration of Prochymal to patients who had failed steroids and multiple other therapies for their severe acute GvHD resulted in significant clinical responses and survival**
- **Prochymal represents a very promising new treatment option**
- **Phase III placebo-controlled clinical trials are underway**