tients and allow for *in vivo* expansion of adoptively transferred EBV-CTL.

Study design: The primary objective of this Phase I clinical trial is to determine the safety of escalating doses of EBV-CTL after CD45 MAbs infusion in EBV-positive NPC patients. The secondary objective is to determine the expansion, persistence and antitumor effects of infused EBV-CTL.

Results: Eight patients with advanced stage, refractory/relapsed NPC have been treated with autologous EBV-CTL (2×10^7-1×10^8 cells/m^2 per infusion). Patients received between 1 - 5 CTL infusions, which were well tolerated, although one developed transient swelling at a pre-existing metastatic disease site. Infusion of CD45 MAbs resulted in a transient period of neutropenia (ANC $<0.5\times10^9$/L), which resolved within 48 hours. The absolute lymphocyte count decreased 4-fold and approached baseline within 14 days post infusion. In 6 of 8 patients, we detected increased IL-15 serum levels, a cytokine important for lymphocyte proliferation. In 3 out of 8 patients EBV-CTL expanded 2.5 to 21-fold within 8 weeks post infusion as determined by IFN-γ Elispot assays. Clinically, 1 patient had a complete response (>9 months), 3 had stable disease for 2 - 16 months, and 4 had progressive disease.

Conclusion: Treatment of EBV-positive NPC with EBV-CTL appears to be safe and can be associated with significant anti-tumor activity. Administration of CD45 MAbs prior to EBV-CTL infusion resulted in transient lymphodepletion and can aid in the expansion of adoptively transferred CTL.

STEM CELL BIOLOGY

82

REGULATION OF INITIAL SELF-RENEWING DIVISIONS OF HEMATOPOIETIC STEM CELLS BY HUMAN MESENCHYMAL STROMAL CELLS

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To identify the signals controlling cell division symmetry and self-renewal of hematopoietic stem cells (HSC) we have studied the cell-cell contact between human HSC and human mesenchymal stem cells (MSC) derived from the marrow, the latter serving as a surrogate "niche" in vitro. By applying novel time lapse microscopy to monitor cell divisions of HSC and correlating cell division symmetry with LTC-IC or myeloid-lymphoid initiating cell (ML-IC) assays at a single cell level, we have previously demonstrated that only vital human MSC were able to drive asymmetric divisions and maintain self-renewal. The roles of specific homing and adhesion molecules, and of junctions between HSC and MSC were studied in the present report. In the first 48 hours, β integrins have been shown to be a major mediator of self-renewing divisions, as well as CXCR4/SDF-1α. However, ligands alone could not recapitulate the effects of MSC. Subsequent to adhesion, junctions are formed between HSC and MSC. At the contact zone, N-cadherin, cadherin 11, protein p120, α- and β-catenin are highly expressed, as demonstrated by immunofluorescence and Westernblot. Gene expression analyses have also shown a significant up-regulation of genes coding for adhesion proteins and extracellular matrix in the adherent subsets of HSC (fibronectin 1, cadherin 11, connexin 43, N-cadherin, ITGBL1, VCAM1 and TGFB1). Upon incubation for further 72 hours, the genes that are up-regulated in the HSC included the checkpoint (CHK1) homolog (CHEK1), early growth response protein 1 (EGR-1) and a number of genes coding for proteins that play a role in proliferation and DNA-repair. Functionally LTC-IC were found almost exclusively among the HSC adherent to MSC. Preliminary data from SCID mouse xenotransplantation model indicated that the slow dividing fraction possessed significantly higher repopulating potential. Thus, albeit homing and adhesion molecules such as β-1- integrins, CXCR4/SDF-1α are essential for mediating the initial cell-cell interactions leading to self-renewal divisions, the formation of junctions and activation of the cadherin-catenin system are essential steps for promotion of self-renewal of HSC by the cellular niche.

SUPPORTIVE CARE

83

INCIDENCE AND MORTALITY OF INVASIVE FUNGAL INFECTIONS IN HIGH-RISK PATIENTS RECEIVING POSACONAZOLE VERSUS FLUCONAZOLE OR ITRACONAZOLE PROPHYLAXIS

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Background: In 2, multicenter, randomized trials (N~1200), the incidence of invasive fungal infection (IFI) and associated mortality were investigated in patients receiving posaconazole (POS) vs fluconazole (FLU) or itraconazole (ITZ).

Methods: In double-blind study, 1600 hematopoietic stem cell transplant (HSCT) recipients with graft-vs-host disease (GVHD) were randomized to receive POS oral suspension (200 mg t.i.d.) or FLU tablets (400 mg q.d.). In study 2, 602 neutropenic patients undergoing chemotherapy for acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS) were randomized to receive either 200 mg t.i.d. oral suspension POS or a standard azole (FLU suspension 400 mg q.d. or ITZ solution 200 mg b.i.d.). The incidence of proven/probable IFI was assessed by a blinded expert panel for the on-treatment phase of study 1 (first dose to last dose plus 7 days) and study 2 (randomization to last dose plus 7 days). Deaths from any cause during both studies were included in the mortality analysis. Cause of death was investigator determined.

Results: In study 1, 600 patients were randomized to receive POS (n=301) or FLU (n=299). In study 2, 602 patients were randomized to receive POS (n=304) or standard azole (FLU [n=240] or ITZ [n=58]). During the on-treatment period, significantly fewer IFIs developed in the POS patient group in both study 1 (2% vs 8%, P=0.004) and study 2 (2% vs 8%, P=0.0009) compared to the FLU or standard azole (FLU or ITZ) groups, respectively. In study 1, prophylaxis with POS resulted in fewer IFIs than with FLU (5% vs 9%, P=0.07) during the primary time period (randomization to day 112). During the period from randomization to day 100 in study 2, POS prophylaxis resulted in significantly fewer IFIs than prophylaxis with FLU or ITZ (5% vs 11%, P=0.003). Fewer cases of aspergillosis developed among patients receiving POS prophylaxis than among FLU or standard azole prophylaxis patients in both study 1 (2% vs 7%, P=0.006) and study 2 (1% vs 9%, P=0.0001). A significant survival benefit was demonstrated in AML/MDS patients receiving POS prophylaxis (study 2) by Kaplan-Meier analysis of time to death by any cause (P=0.035).

Conclusion: In these 2 studies, prophylaxis with POS resulted in fewer IFIs than prophylaxis with FLU or ITZ. Mortality rates in both studies were higher in patients who developed an IFI than in patients who did not, indicating that prophylaxis is a strategy that prevents mortality in high-risk patients.

Overall Mortality During Study

	Patients With IFI		Patients Without IFI	
	Study 1	Study 2	Study 1	Study 2
	n = 62	n = 32	n = 538	n = 570
Deaths, n (%)	40(65)	12(38)	120(22)	104(18)
Primary cause of death				
IFIs	13(21)	8(25)	3(1)*	13(20)*
Underlying disease (GVHD/malignancy)	10(16)	2(6)	54(10)	43(8)
Other complications	17(27)	2(6)	63(12)	48(8)

*Death attributed to IFI by investigator, but not considered due to IFI by blinded expert panel