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UMBILICAL CORD BLOOD IMMUNOTHERAPIES

Umbilical cord blood–derived cellular products for cancer immunotherapy

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Abstract

Although the vast majority of experience with umbilical cord blood (CB) centers on hematopoietic reconstitution, a recent surge in the knowledge of CB cell subpopulations as well as advances in *ex vivo* culture technology have expanded the potential of this rich resource. Because CB has the capacity to generate the entire hematopoietic system, we now have a new source for natural killer, dendritic and T cells for therapeutic use against malignancies. This Review will focus on cellular immunotherapies derived from CB. Expansion techniques, ongoing clinical trials and future directions for this new dimension of CB application are also discussed.

Key Words: *cancer immunotherapy, cellular therapy, cord blood, expansion*

Introduction

Over the past several decades, the use of cellular immunotherapy has increased significantly in the adjuvant treatment of cancer. Such cell-based immunotherapies include allogeneic hematopoietic stem cell transplantation (HSCT), T-cell and natural killer (NK)-cell adoptive transfer and dendritic cell (DC)-based vaccination. Traditionally, these cellular therapeutic products are directly isolated from peripheral blood (PB) and infused into the cancer patient after brief activation or *ex vivo* expansion. Alternatively, clinically appropriate doses of these cellular therapeutic products can be differentiated and expanded *ex vivo* from $CD34^+$ hematopoietic stem and progenitor cells (HSPCs). In this context, different sources of HSPCs have been exploited, including bone marrow (BM), mobilized peripheral blood HSPCs, umbilical cord blood (CB) and even human embryonic stem cells.

In particular, umbilical CB provides a rich source of HSPCs from which high numbers of therapeutic cells can be generated with potent immune effector functions. Exploiting CB for this purpose has the advantage of non-invasive collection, less stringent HLA matching and off-the-shelf availability of large number of units from CB banks worldwide. Rapid advancement in new protocols supporting NK cell, DC and T-cell generation under Good Manufacturing Practice (GMP) conditions has granted the potential for treatment of cancer patients, thereby overcoming the limitations of low therapeutic cell numbers and poor activation/maturation state of PB-derived cellular products. This Review focuses on novel cellular immunotherapies derived from umbilical CB, including expansion techniques, ongoing clinical trials and future directions for this new dimension of CB application.

CB-derived NK cells

In the rapidly evolving era of immunotherapy, NK cells have emerged as exciting candidates for allogeneic cellular therapy. Allogeneic NK cells are thought to kill tumor cells through disinhibition of inhibitory killer-like immunoglobulin receptors

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Table I. Overview of current recruiting trials with adoptive transfer of allogeneic NK cell products.

NK cell product	Trial identifier	Disease	Study phase	No. of patients	Age (years)	Relevant information	Combined therapy
Haplo-identical allogeneic PB-NK cells	NCT01576692	Neuroblastoma	Phase I	20	Childhood	Children with relapsed or refractory neuroblastoma	Humanized anti-GD2 antibody
	NCT02118285	Ovarian cancer		20	>18	Patients with recurrent tumor. Intra-peritoneal NK infusion	Oral IDO inhibitor INCB024360
	NCT00569179	Hematological cancers (AML)		24	18–65	Single NK infusion after allo-SCT	Allo-SCT
	NCT01385423	Hematological cancers (AML)		34	>18	Safety study for IL-15, with evaluation of NK expansion after adoptive transfer	IL-15
	NCT02130869	Solid tumors and lymphoma		36	Childhood	Children with high-risk solid tumors for whom autologous transplantation is indicated	Anti-GD2 antibody (hu14.18K322A) also given in patients with neuroblastoma
	NCT00877110	Neuroblastoma		72	–	High-risk patients	Anti-GD2 3F8 antibody
	NCT01287104	Solid and hematological cancers		86	4–35	NK cell infusion on days 7 and 35 after HSCT	Allo-SCT
	NCT00789776	Hematological cancers	Phase I/II	35	–	Donor NK infusion at day 7 after allo-SCT, after Cy/Flu/TBI	Allo-SCT
	NCT01823198	Hematological cancers (AML, MDS)		72	<65	NK infusion at day 8. Dose escalation up to 100 mol/kg	Allo-SCT
	NCT01795378	Hematological cancers (AML)		85	>17	Refractory AML	Allo-SCT
	NCT02074657	Hematological cancers	Phase II	10	Childhood	Relapse or refractory AML	–
	NCT02259348	Hematological cancers		18	Childhood	NK cell infusion before allo-SCT in patients unsuccessful in previous SCT	Allo-SCT
	NCT02100891	Solid tumors (including neuroblastoma)		20	–	Allogeneic bone marrow transplant preceded by reduced-intensity chemotherapy and radiation therapy, followed by donor NK cells on day +7 after transplant	Allo-SCT
	NCT01181258	Hematological cancers		34	–	Refractory NHL and CLL	Rituximab
	NCT01700946	Hematological cancers		40	<21	–	Rituximab, allo-SCT
	NCT01857934	Neuroblastoma		42	<18	Allo-SCT after reductive surgery, NK infusion early after transplant	Allo-SCT, anti-GD2 antibody
	NCT01593670	Hematological cancers (MDS)		46	18–75	High-risk MDS. Pre-treatment with decitabine (10 mg, IV, 5 days) and NK infusion at day 17	Decitabine and vorinostat
	NCT02229266	Hematological cancers (AML)		56	>65	High-risk AML patients in remission after first chemo non-eligible for SCT	–
	NCT00145626	Hematological cancers		66	Childhood	Donor-derived-NK infusion 1 week after allo-HSCT	Allo-SCT
	NCT01807611	Hematological cancers		110	<21	High-risk patients in first complete remission	Allo-SCT
	NCT00703820	Hematological cancers (AML)	Phase III	270	<21	Standard-risk AML with different conditioning tested before NK infusion	–