IMMUNOTHERAPY FOR LYMPHOMAS

Essay

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Abstract

Key Words : immunotherapy, Lymphoma, targeted therapy.

Lymphomas represent the fifth most common cancer diagnosis. Therapies of lymphomas are moving away from the non-specific cytotoxic agent, toward more targeted approaches including immunotherapy. Immunotherapy approaches include monoclonal antibodies either alone or combined with chemotherapy or radiotherapy and the use of cytokines and anti-lymphoma vaccines which are still under trial.

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List of Abbreviations

ADCC	antibody-dependent cellular cytotoxicity
AILT	Angioimmunoblastic T-cell lymphoma
Aut.BMT	autologus bone marrow transplantation
BALT	bronchial-associated lymphoid tissue
B-CLL	B-chronic lymphocytic leukemia
BCNU	1,3-Bis(2-Chloroethyl)-1-NitrosoUrea
Bi-Mabs	Bispecific molecules
BSMs	Bispecific monoclonal antibodies
CALLA	common acute lymphoblastic leukaemia antigen
CD	cluster of differentiation
CDC	complement dependent cytotoxicity
CR	Complete response
CR	complete remission
CSF	Cerebrospinal fluid
CTL	cytotoxic T-lymphocytes
DC	dendritic cell
DLBCL	diffuse large B-cell lymphoma
EBNA	EBV nuclear antigens
EBV	Epstein barr virus
ECOG	Eastern Cooperative Oncology Group
EFS	event free survival
Fab	fragment for antigen binding
Fc	fragment crystallizable
FDA	The food and drug administration
GALT	gut-associated lymphoid tissues
GELA	Groupe d'Etude des Lymphomes de l'Adulte
GM-CSF	granulocyte-macrophage colony stimulating factor
GPI	Glycosylphosphatidylinositol
HAART	highly active anti-retroviral therapy
HACA	human anti-chimeric antibody
HAHA	human anti-human antibody
HAMA	human anti-mouse antibody
HCV	Hepatitis C virus
HDCT	high dose chemotherapy
HEV	high endothelial venules
HHV-8	human herpes virus-8

HL	Hodgkin's lymphoma
HLA	human leucocyte antigen
H-RS	Hodgkin-reed sternberg
HSCT	hematopoietic stem-cell transplantation
HTLV-1	Human T-cell leukemia virus-1
I-131	Iodine-131
Id	idiotype
Ig	Immunoglobulin
IgH	Immunoglobulin heavy chain
IL-2	Interleukin-2
ILSG	International Lymphoma Study Group
INF	Interferon
IPI	International prognostic index
ITs	immunotoxins
KLH	keyhole limpet hemocyanin
KSV	Kaposi's sarcoma virus
LDH	lactate dehydrogenase
LGLs	large granular lymphocytes
LPHL	lymphocyte predominance Hodgkin's lymphoma
MAb	Monoclonal antibody
MAGE-1	the melanoma antigen gene -1
MALT	mucosal-associated lymphoid tissue
MCL	mantle cell lymphoma
MDR	multidrug resistance
MHC	major histocompatibility complex
MUC-1	mucin peptide core -1
NCI	National Cancer Institute
NHL	non-Hodgkin's lymphoma
NK	natural killer cells
PALS	periarteriolar lymphoid sheath
PCR	polymerase chain reaction
PD	Progressive disease
PET	Positron emission tomography
PR	Partial response
REAL	the Revised European-American Lymphoma classification
RIT	radioimmunotherapy
rIT	recombinant immunotoxin
Rth	Radiotherapy
scFv	single-chain variable region
SD	Stable disease
SLL	small lymphocyte lymphoma

TBI	total body irradiation
TCR	T cell receptor
TNF-α	tumer necrosis factor-α
T-PLL	T-prolymphocytic leukemia
WHO	The World Health Organization
WM	Waldenström's macroglobulinemia
Y-90	Yttrium-90

INTRODUCTION

Introduction

The lymphomas are a diverse group of malignant disorders that vary with respect to their molecular features, genetics, clinical presentation, treatment approaches, and outcome. They represent one of the most important health problems which accounts for about 4% of the new cases of cancer diagnosed each year, making them the fifth most common cancer diagnosis and the fifth leading cause of cancer death. In fact, while the incidence of most cancers is decreasing, lymphoma is one of only two tumors increasing in frequency, although the cause for this increase is unknown. An exiting issue now is the management of patients with lymphomas using new therapeutic strategies that are moving away from the nonspecific cytotoxic agents and toward more targeted approaches ***(Cheson, 2004).***

Traditional approaches for treatment of lymphomas include radiotherapy, chemotherapy, and bone marrow transplantation. More than one of these approaches may be used in the management of cases of lymphoma. The challenge is to determine a course of therapy that preserves cure while minimizing long-term complications ***(Emmanouilides and Casciato, 2004).***

Recent years have witnessed the development of a variety of promising immunotherapies for treating patients with lymphomas. Foremost among these advances is the exciting success of monoclonal antibodies directed against lymphocyte surface antigens. This antibody therapy has now become an important part of our therapeutic armamentarium for lymphoma. Several monoclonal antibodies have been approved by the food and drug administration (FDA) and are in widespread use either alone or in combination with chemotherapy,

radiotherapy or with other biologic agents. In addition to monoclonal antibodies, other passive therapies with various immune cell populations and cytokines are under investigation ***(Maloney, 2005).***

Moreover, active immunotherapy, whereby the host is induced to make an immune response against its own tumor cells, has long been a goal of tumor immunologists. At the present time no active immunotherapy maneuver has proven to be routinely effective in the clinic, but intense efforts are underway to develop such an approach ***(Levy and Timmerman, 2001).***

The current essay was conducted to delineate advances, problems and prospects for approaches to anti- lymphoma immunotherapies.

OVERVIEW
OF
LYMPHOID SYSTEM

Overview of the lymphoid system

The human immune system has the capacity to identify and respond specifically to invading pathogens. It can also 'remember' the exposure, such that subsequent exposure to the same pathogen results in a more rapid and potent immune response. Lymphocytes play the key role in the adaptive immune response, mediating both specificity and memory ***(Degar and Berliner, 2003).***

Lymphoid organs can be divided broadly into central or primary lymphoid organs, where lymphocytes are generated, and peripheral or secondary lymphoid organs, where adaptive immune responses are initiated and where lymphocytes are maintained. The central lymphoid organs are the bone marrow (the human equivalent of the avian bursa of Fabricius) and the thymus(an organ in the upper chest), whereas the peripheral lymphoid organs are the lymph nodes, the spleen, and the mucosal lymphoid tissues ***(Janeway et al., 2005).***

The **lymph nodes** are highly organized lymphoid structures located at points of convergence of vessels of the lymphatic system, which is an extensive system that collects extracellular fluid from the tissues and returns it to the blood. This extracellular fluid is produced continuously by filteration from the blood and is called **lymph**. The vessels are **lymphatic vessels** or **lymphatics**. **Afferent lymphatic vessels** drain fluid from the tissues and also carry antigen-bearing cells from infected tissues to the lymph nodes, where they are trapped. In the lymph nodes, B lymphocytes are localized in follicles, whereas T cells are more diffusely distributed in surrounding **paracortical areas**, also referred to as **T-cell zone**. Some of the B-cell follicles include **germinal centers**, where B cells are undergoing intense proliferation after encountering their specific antigen and their cooperating T cells. B and T

lymphocytes are segregated in a similar fashion in other peripheral lymphoid tissues, and this organization promotes the crucial interactions that occure between antigen-presenting cells and T cells, and between antigen-specific T cells and B cells upon encountering antigen ***(Gowans, 1996).***

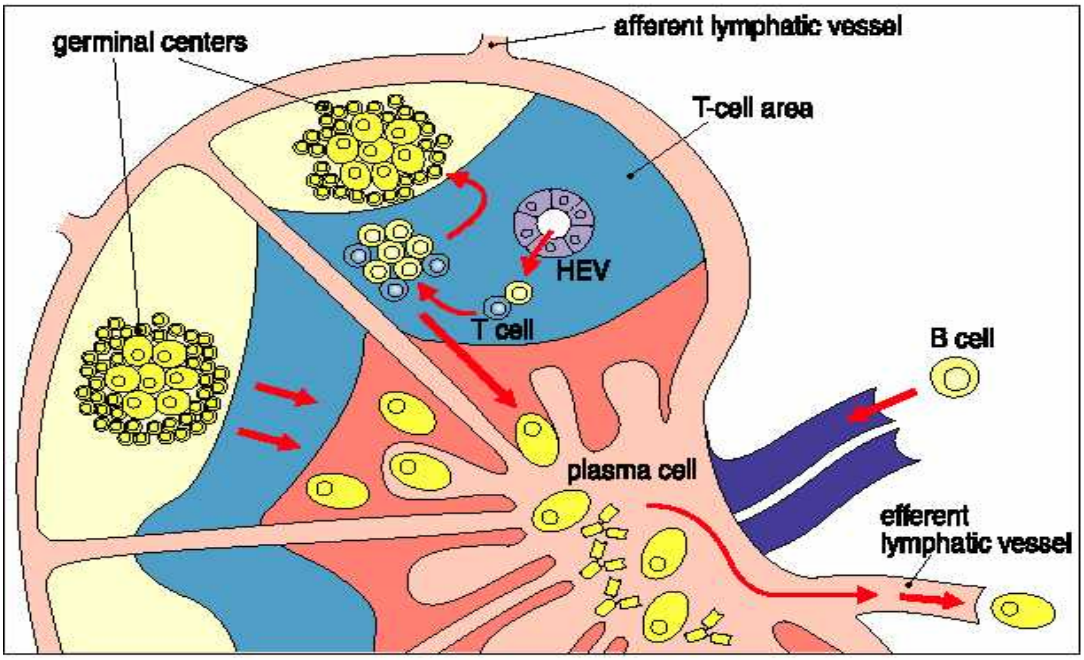

Figure1. *Organization of a lymph node* ***(modified from Janeway et al., 2005)***

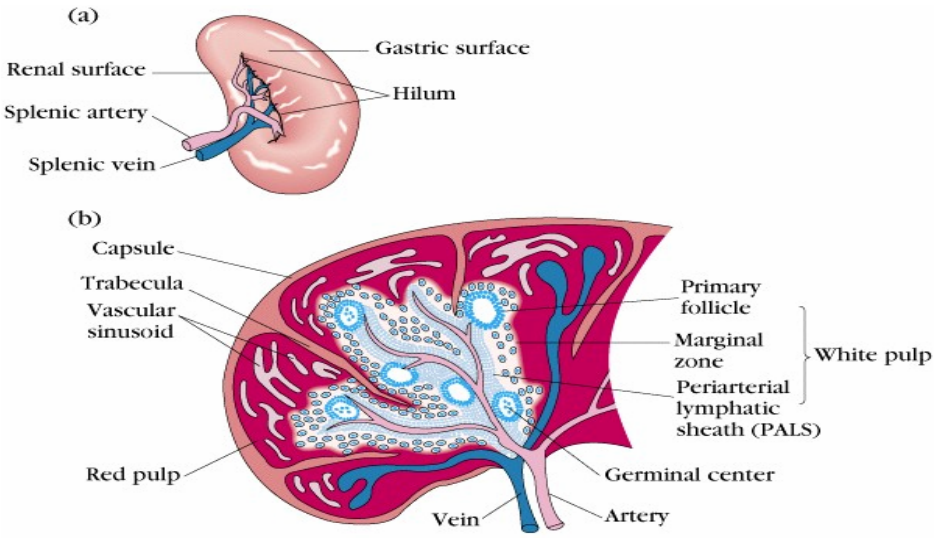

Figure 2. *Organization of the lymphoid tissues of the spleen* ***(modified from Janeway et al., 2005)***