Cytokines: Interferons, Interleukins and Beyond

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Learning Objectives

- Understand the nature of cytokines and cytokine effects on immune cells.
- Identify cytokines that are currently used for cancer immunotherapy
- Describe the rationale for considering IL-2 immunotherapy.
- Identify the main patient selection criteria for IL-2-based immunotherapy.
- Recognize the manifestations of toxicity related to IL-2 administration.
- Consider cytokines as potential biomarkers in cancer

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Overview

- Primer on characteristic features of cytokines
- Cytokines in the immune system
- Focus on IL-2 (Aldesleukin; prototype cytokine)
  - Clinical applications
  - Toxicity
  - Clinical response
- Cytokines as biomarkers of cancer progression

What are cytokines?

- A diverse family of immune regulators transiently produced by a variety of cell types:
  - Interleukins
  - Interferons
  - Tumor necrosis factors
  - Chemokines
- The number of known cytokines has been rapidly expanding
- Cytokines bind to **cell surface receptors** on target cells and influence:
  - Gene transcription and activation (of other cytokines)
  - Proliferation
  - Cytotoxicity
  - Immunological memory
  - Movement of cells into sites of inflammation

General characteristics of cytokines

- Cytokines are small proteins or glycoproteins which play a critical role in the pathogenesis of human diseases
- Cytokines are local mediators, meant to exert biologic effects in their microenvironment
- Systemic effects of cytokines are frequently quite different and more dramatic than those mediated locally
- Cytokines are pleiotropic and redundant
- Cytokines work as cascades, and a "cytokine profile" best defines their presence in a constellation of soluble factors produced by cells
- A "cytokine profile" is often dramatically altered in disease (cytokine polarization)

More Details

A list of cytokines and chemokines grouped by their receptor types

- Interleukins
  - Class I receptors: γ-chain (**IL-2**, IL-4, IL-7,IL-9,IL-13, IL-15, IL-21);
    β-chain (IL-3, IL-5, GM-CSF);
    IL-6 like (IL-6, IL-11, IL-30, IL-31);
    IL-12 family (IL-12, IL-23, IL-27, IL-35)
  - Class II receptors: IL-10 family (IL-10, IL-19, IL-20, IL-22, IL-24, IL-26, IFN type III)
  - Ig superfamily or IL-1 receptor family: (IL-1α, IL-1β, IL-1RA, IL-18)
  - IL-17 receptor family: (IL-17, IL-25)
- Interferons (around 36 total)
  - Type I: Alpha, Beta (IFNAR1, IFNAR2)
  - Type II: Gamma (IFNGR1, IFNGR2)
  - Type III: Lambda
- Chemokines
  - CCL (CCL1 – CCL28)
  - CXC family
- TNF receptors (p55 and p75) family: (TNF-α, LT-α, LT-β, FasL, CD40L, TRAIL,LIGHT)
- TGF-β receptors (Type1 &Type2)

Comment: Structural features (shared subunits) of some (not all) cytokine receptors permit cytokine grouping into families

Cytokines That Have Been Tested in Humans

- IL-1-α
- IL-1-β
- **IL-2**
- IL-4
- IL-7
- IL-12
- IL-15
  IL-18
- IL-21
- **Interferons**
- TNFs

Only IL-2 and the Type I IFNs have thus far been approved for clinical use

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Biological effects of interferons

- Bind to receptors present on a wide variety of cells
- Anti-viral effects
- Anti-proliferative effects
- Anti-tumor effects
- Major histocompatibility complex regulation
- Natural and recombinant interferons are now approved as effective therapies for a variety of cancers, hepatitis and papilloma virus infections and multiple sclerosis

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EDITORIAL

Present Status and Future Prospects for Adjuvant Therapy of Melanoma: Time to Build upon the Foundation of High-dose Interferon Alfa-2b

Stergios J. Moschos, John M. Kirkwood, University of Pittsburgh Cancer Institute, Pittsburgh, PA Panagiotis A. Konstantinopoulos, State University of New York Upstate Medical Center, Syracuse, NY

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Interferon Immunotherapy

- Remains the only FDA-approved adjuvant therapy for stage III melanoma
- Relapse-free survival consistent across 30 years of investigation
- Overall survival benefit remains controversial (3 – 5% range and not with low dose regimens)
- Findings of ECOG 1609 (IFN vs Ipilimumab in stage III melanoma) will be of interest.

IL-2 History

1965 Factor stimulating DNA synthesis derived from lymphocyte cultures[1]

1976 Factor identified as a T-cell growth factor[2]

1983 First clinical use of lymphocyte-derived IL-2 for melanoma[3]

1984 Clinical trial of cell-line-derived IL-2 in cancer and AIDS[4]

1984 rIL-2 produced in *E coli* demonstrated the same range of biological activity as native IL-2[2]

1985 Clinical trials with rIL-2 for advanced malignancies[2]

1992 rIL-2 (aldesleukin) approved for metastatic RCC

1998 rIL-2 (aldesleukin) approved for metastatic melanoma

Major Selection Criteria for IL-2

- Metastatic renal cancer or melanoma
- Normal pulmonary and cardiac function as assessed by PFTs and ETT
- “Relatively” normal renal and hepatic function
- Controlled brain metastases
- No active infection
- No active autoimmune disease requiring steroids (vitiligo and autoimmune hypothyroidism OK)

IL-2 Treatment

- IL-2 = 600,000 international units per kg IVB x 14 planned doses.
- Manage clinical consequences of immune activation.
- Second cycle given after 2 week break. Scans repeated one month later.
- More IL-2 for lucky responders (up to 3 courses (6 cycles) maximum).

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IL-2 Side Effects

Immunotherapy with high-dose IL-2 has serious side effects

- Constitutional (flu-like)
- Cardiovascular
- Gastrointestinal
- Pulmonary
- Metabolic
- Neurologic
- Hepatic
- Renal
- Dermatologic
- Capillary leak
- Hematologic/ immunologic

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IL-2 Toxicity

HYPOTENSION

Cardiac Tachy or Bradydysrhythmias

FATIGUE

RENAL FAILURE

Hepatic Dysfunction

RASH

ACIDOSIS

Weight gain/Fluid Retention

Hypothyroidism

Hypoxia

Pleural effusions

Desquamation

DIARRHEA

Lymphopenia

Mucositis

Splenomegaly

Peripheral neuropathy

Pulmonary Infiltrates

HEART ATTACK

Vomiting

ITCHING

NAUSEA

Arthralgias/myalgias

Thrombocytopenia

VITILIGO

Hyperbilirubinemia

Stroke-like syndromes

Mental status changes

Infection

Electrolyte abnormalities

CHILLS

Anorexia

Abdominal visceral perforation

Vivid Dreams

DEATH

Bleeding/Clotting

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Physiology of IL-2-Induced Capillary Leak

- Nitric oxide
- TNF, IL-1 (“cytokine storm”)
- Lymphocyte activation and movement through blood vessels
- Activation of prostaglandin pathways

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Criteria to Consider Stopping IL-2

- Uncontrolled sinus tachycardia >150
- EKG changes of ischemia
- Uncontrolled atrial fibrillation/supraventricular tachychardia
- Ventricular arrhythmias
- Elevated CPK-MB
- Moist desquamation
- Diarrhea 1000 cc/shift $\times$ 2
- Vomiting unresponsive to medication
- Severe abdominal distention affecting breathing
- Severe abdominal pain, unrelenting
- Phenylephrine
  - 3.0 µg/kg/min
  - Prolonged need for high doses
- Frank blood in sputum, emesis, stool
- Platelets <30,000/µL
- Strong clinical suspicion of or documented infection

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Why do we offer this difficult (barbaric) treatment?

Implementation of an Interleukin-2 National Registry: an opportunity to improve cancer outcomes

Michael K Wong[1*], Howard L Kaufman[2*], Gregory A Daniels[3], David F McDermott[4], Sandra Aung[5], James N Lowder[5] and Michael A Morse[6]

Journal for ImmunoTherapy of Cancer

Durable responses and reversible toxicity of high-dose interleukin-2 treatment of melanoma and renal cancer in a Community Hospital Biotherapy Program

Roxanne Payne[1], Lyn Glenn[1], Helena Hoen[1], Beverley Richards[1], John W Smith II[2], Robert Lufkin[2], Todd S Crocenzi[1], Walter J Urba[1] and Brendan D Curti[1*]

High dose interleukin-2 (Aldesleukin) - expert consensus on best management practices-2014

Janice P Dutcher[1*], Douglas J Schwartzentruber[2], Howard L Kaufman[3], Sanjiv S Agarwala[4], Ahmad A Tarhini[5], James N Lowder[6] and Michael B Atkins[7]

HD IL-2 extends OS in malignant melanoma
April 18, 2015

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Conclusions for IL-2

- IL-2 can be administered safely at sites experienced in cytokine toxicity management.
- Patients have significant, but reversible toxicity during IL-2.
- Objective responses occur that translate into a survival benefit in selected patients with melanoma and renal cell carcinoma.

Cytokines in biotherapy trials

- Assessments of pharmacokinetics
- Rigorous sample collection and storage to avoid cytokine degradation
- Serial monitoring of changes in cytokine profiles in the plasma (multiplex assays)
- Correlations of cytokine profiles with immune responses and clinical end points
- A requirement for expert statistical analysis for result interpretation

Cytokines as biomarkers in cancer

Prognostic value of circulating cytokines on overall survival and disease-free survival in cancer patients

- Recent meta-analysis data from clinical trials: clinical cytokine profiles associated with immune stimulation and immune suppression have a prognostic value
- IL-6 and related cytokines emerge as critical lynchpins between inflammation and cancer
- Cytokines modulate functions of immune cells and these immunomodulatory activities translate into clinical outcome