Cytokines in Cancer Therapy

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Cytokines – What are they?

- Endogenous substances
- Hormones within the immune system
- Sending messages between immune cells, mediated by receptors
- Some direct effects on tumors and infections
- Stimulation of growth of cells in immune system
Actions of Cytokines

- Regulate normal cell function; regulate receptor expression
- Immune mediators
- Growth stimulating factors
- Growth inhibition
- Induction or inhibition of various cell regulatory proteins
Cytokines in Cancer Therapy

• Therapeutic Cytokines
  – Alpha/Beta Interferons
  – Interleukin-2
  – Gamma Interferon
  – Interleukin-12

Hematopoietic Growth Factors
  - GM-CSF
  - G-CSF
Cytokines in Cancer Therapy

• Cytokines that stimulate some tumor cell growth
  – IL-6 – myeloma; ? RCC
  – IL-1 - CML

• Cytokines that induce toxicity during treatment
  – IL-1
  – TNF
  – Gamma Interferon
INTERFERONs (IFN)  
Alpha, Beta, Gamma  

• “Interfere” with viruses
• Type I – α, β – same receptor  
  – Anti-Viral Defense  
  – Inhibit Viral Proliferation  
  – Anti-proliferative effect on normal and tumor cells
• Type II - γ – Immune interferon  
  – Immune modulation
• Induce new proteins- new cell products  
• Suppress oncogenes
ACTIONS OF INTERFERONS

• Suppression of Apoptosis
• Phosphorylation of nuclear proteins, greater than 30 interferon-stimulated genes
• Anti-angiogenic activity
• Anti-oncogene activity: downregulation of c-myc, c-src, c-ha-ras
MAJOR BIOLOGICAL ACTIVITIES OF IFN-α /β

• Anti-viral effect
• Inhibition of cell growth and replication
• Modulation of expression of MHC I and to lesser extent MHC II
• Stimulation of macrophage, CTL, and NK activity
• Anti-tumor activity
IMPORTANT PROTEINS INDUCED by IFN-α and IFN-β

• MHC Class I
• B-2 Microglobulin
• MHC Class II
• Metallothionein II
• Many others
IFN and Tumor Cells

- Anti-proliferative – particularly demonstrated in vitro
- Differentiation – particularly noted in leukemia cells and B-cell derived cells
- Mechanism of cell kill in solid tumors not clear
- Kaposi’s sarcoma - ? Anti-viral
IFN-α, Cancer Therapy

• Hematopoietic Malignancies – Anti-proliferative effect, among others

• Chronic myeloid leukemia, hairy cell leukemia, cutaneous T-cell lymphoma, myeloma, B-cell non-Hodgkin’s lymphoma
IFN-α in Hematologic Malignancies

- Rarely, complete cytogenetic remission in CML
- Complete Remission in HCL
- Remission in CTCL
- Maintenance in Myeloma, NHL - controversial
IFN-α in Solid Tumor Therapy

- Melanoma – Adjuvant Therapy – prolongs time to recurrence; no survival difference
- Melanoma – Advanced Disease – some regressions; prolongation of stable disease
- Renal Cell Cancer – Advanced Disease – some regressions; prolongation of stable disease
Interferon + Chemotherapy

- Interacts with more than 20 agents
- Increases or decreases in metabolism of chemotherapeutic agent
- Modulation of activity
- No data so far, of synergy
IFN Administration

- Subcutaneous injection
- Daily, low dose, schedule (hepatitis), CML
- Three times weekly, higher doses, solid tumors
- Doses range from 3 MU/day to 10 MU/tiw, to 20 MU daily for 1 month
IFN Side Effects

• Fever, Chills following injection
• Flu-like syndrome, myalgias, arthralgias, loss of appetite, headache, lethargy
• Cumulative Fatigue
• Weight loss – may be as much as 20 lbs over a 6 month course
• Managed symptomatically
IFN Side Effects

• Older patients – may become confused, and may have significant decline in performance status
• Chronic fatigue may cause incapacitation
• Rare – neuropathy
• Rare - retinopathy
Interleukin-2 (IL-2)

- T-cell growth factor
- Activates killer T-cells and natural killer cells
- Clonal expansion of effector T-cells responding to original antigen
- Cell-mediated tumor cell death
- Signals release of secondary cytokines:
  - IL-1, TNF, Gamma-IFN
IL-2 Based Therapy

• Cell-mediated cytotoxicity
• Demonstrated in vitro when tumor cells are exposed to activated lymphocytes
• Requires immune cells for tumor lysis
• 99% killing of tumor cells in vitro
IL-2 - in vitro and Animal Model Activity

- Methylcholanthrine induced sarcomas
- Colorectal cancer cells
- Melanoma
- Renal Cell – Renca model
- Leukemia
- Lymphoma
- others
IL-2 Administration

• High Dose, intensive short course (2 wks)
• Moderate Dose, intravenous bolus or continuous infusion, short course (2 wks)
• Subcutaneous injections – daily x 5 or tiw, prolonged course (6 months)
Eligibility For HD IL-2

- No medical contraindications
- Metastatic RCC or Melanoma
- In-curable disease
- Meets cardiac and pulmonary criteria for this type of treatment
- No active brain metastases
HIGH DOSE IL-2 SCHEDULE

- WEEK 1
- 600,000 to 720,000 U/kg
every 8 hours by short IV infusion
  5 days treatment
  up to 14 doses
  9 DAY BREAK

WEEK 2
600,000 to 720,000 U/kg
Every 8 hours by short IV infusion
  5 days treatment
  up to 14 doses
Other Doses and Schedules

- Moderate Dose IV: 72,000 U/kg every 8 hours for up to 14 doses (5 days), then 9 day break, then another 5 days (up to 14 doses)
- Subcutaneous: 5 MU/m2 daily; 18 MU/m2 days 1-3, 11 MU/m2 days 4-5, weekly x 4 weeks, then 2 week break, then repeat. New variations are tiw dosing
HD IL-2 Toxicities

- Hypotension, capillary leak syndrome
- Tachycardia, rarely arrhythmias
- Oliguria, azotemia
- Fever, Chills, lethargy
- Itching, erythematous rash
- Nausea, vomiting, diarrhea (minority of pts)
HD IL-2 Toxicities, cont

- Liver function test abnormalities
- Prolongation of INR (coagulopathy)
- Thrombocytopenia (rare, more in those having had prior chemotherapy)
- Leukocytosis
- Neurotoxicity – Confusion/agitation
IL-2 Toxicities – lower doses

- Moderate dose bolus – much lower grade, but similar to HD IL2
- Subcutaneous chronic administration - Constitutional symptoms – fever, chills, nausea, diarrhea, lethargy, fatigue, weight loss, loss of appetite; rarely – dehydration, confusion
# IL-2 THERAPY FOR RCCA: TUMOR RESPONSE

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# IL-2 THERAPY FOR RCCA: PATIENT OUTCOME

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#Excludes Surgical intervention
**IL-2 Therapy**

- Produces durable complete responses in stage IV melanoma and renal cell cancer – some lasting multiple years

- This is the only treatment to do this in a solid tumor (except testicular cancer, a congenital cancer)
HD IL-2 Therapy: PLA Data Base: Response Durations-255 patients

Fisher et al J Sci Amer 1997
IL-2 Activity – Other Metastatic Malignancies

- Colon Cancer – CR’s and PR’s – same rate as with 5-FU
- Breast Cancer, PR’s
- Lymphoma, Hodgkin’s disease – PR’s
- Data from NCI and CWG broad phase II trials in 1980’s; no further f/u
IL-2 Activity in Leukemia

• NK and LAK activity can be induced in patients with acute leukemia
• LAK activity is greater in patients in remission than in patients with active leukemia
• In vitro induction of LAK activity against leukemic cells and in murine models
IL-2 Activity in Leukemia

• Circulating NK/LAK cells following allo- or autologous BMT
• IL-2 in this setting, augments NK/LAK cell number and activity
• Increased numbers of NK/LAK cells with cytotoxicity to leukemic cells are present, after post-chemo IL-2 administration
IL-2 in Myeloid Leukemia, Maintenance after 2nd Remission

• Peg IL2 weekly, 3 of 7 had 2nd CR more than twice as long as 1st CR (2 pts for > 10 years) (Dutcher, et al)

• IL-2 9 MU/m2 IV daily x 5 x 2 wks, 4 wk rest, then repeat (total of 4 cycles) - Median CR 14 mo; 4/12 pts 2nd CR >> than 1st CR (Bergman, et al)
Other Cytokines Studied in Cancer

• IL-4 – low grade B-cell malignancies – PR’s, MR’s in small numbers of patients
• IL-6 – solid tumors – minimal activity
• IL-12 – Proliferation, differentiation, and activation of killer cells – anti-tumor activity in RCC, Melanoma, CTCL, but toxicity stopped further development
• IFN –γ – not active in vivo
Cytokines in Development

- IL-18 – planning clinical trial in melanoma
- Antagonists to IL-6 being evaluated
- Antagonists to IL-1 and TNF are in clinical use
Summary

• IFN-α and IL-2 have become mainstays in clinical therapy of cancer for the past 20 years
• Full understanding of mechanism, and why they work only in some patients is unknown
• Further mechanistic work is needed
• Consider re-exploration in other malignancies