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
- Β-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

	IL-2	IL2/IFN	IL2/IFN	5FU/IL2/IFN
N	71	28	47	50
CR	6	0	2	2
PR	6	3	6	7
RR	17%	11%	17%	18%
Duration(mos)				
median	53	7	12	9
range	(4-84+)	(7-14)	(1-56+)	(3-53+)
Survival				
median (mos)	15.5	16	20.4	17.5

IL-2 THERAPY FOR RCCA : PATIENT OUTCOME

	IL-2	IL2/IFN	IL2/IFN	5FU/IL2/IFN
No. Pts	71	28	47	50
med f/up (mos)	84	84	48	48
Alive n (%)	10 (14%)	3 (11%)	4 (8.5%)	7(14%)
Cont Resp	4	0	1	1
Surg NED	1	1	0	4
PD	5	2	3	1
PFS 3yr	13%	3%	2%	10%
PFS # 3yr	9%	3%	2%	2%

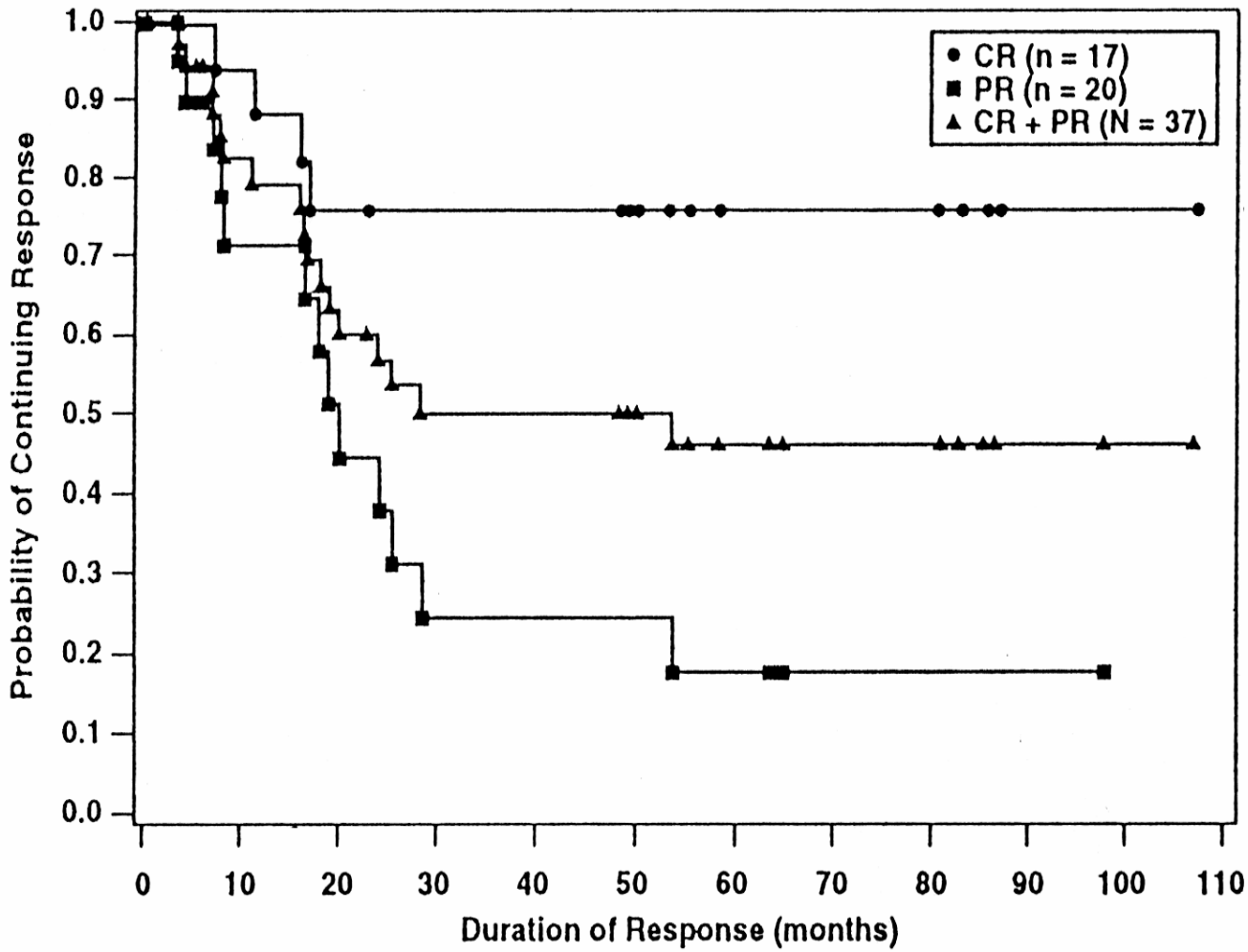
#Excludes Surgical intervention

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 et al J Sci Amer 1997

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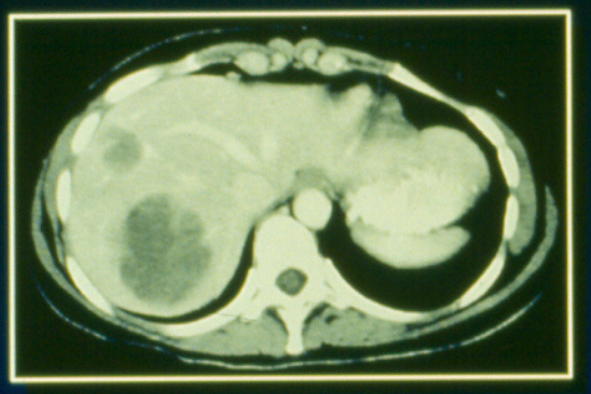
Pre-treatment



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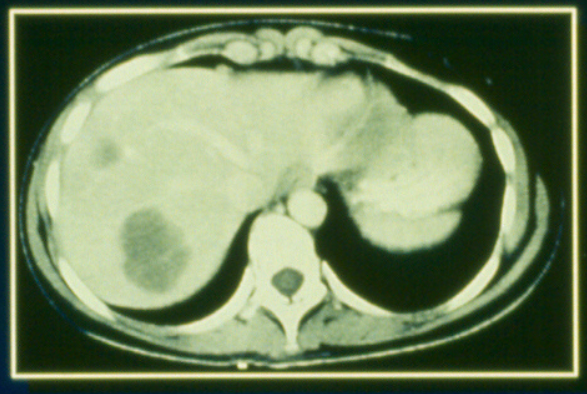
Post-treatment



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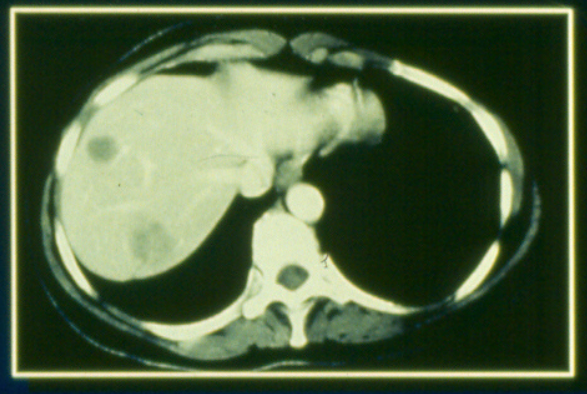

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IL-2 Activity – Other Metastatic Malignancies

- 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 autolgous 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