Cytokines: Interferons, Interleukins and Beyond

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Disclosures

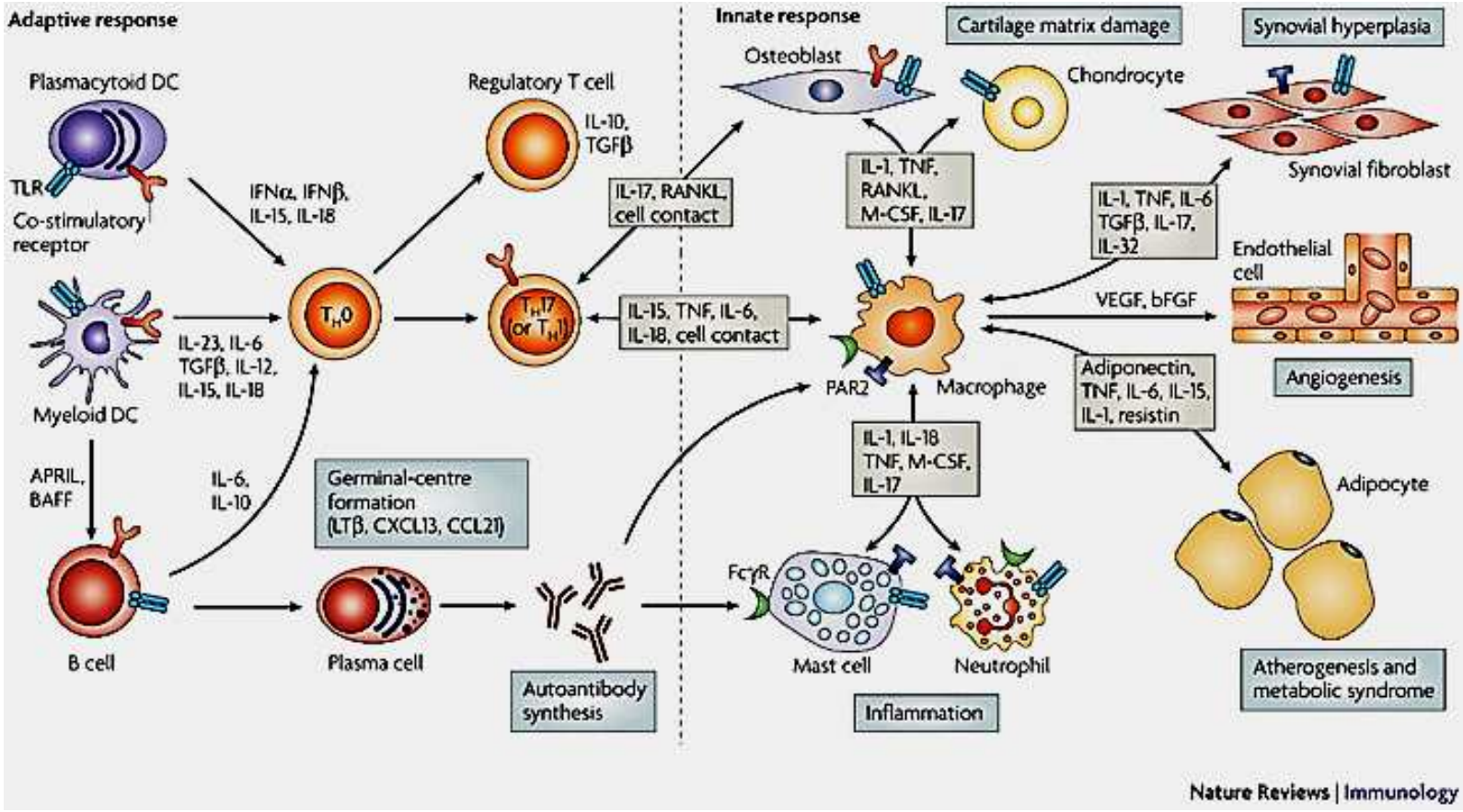
- No potential conflicts of interest.

- There will be discussion about the use of products for non-FDA approved indications in this presentation.

Brief Review of Nomenclature

- Cytokines
- Interleukins
- Interferons
- Chemokines
- Hemopoietic Growth Factors

Cytokines: Immune Messengers



Nature Reviews Immunology 2007, 7: 429-442

Published evidence for specific cytokine expression in various cancer types

	Lung	Breast	Colorectal	Gastric	Malignant melanoma	Pancreatic	Malignant glioma	Hepato cellular	Renal cell	Head and neck	
Macrophage migration inhibitory factor expressed in cancer tissue	+	+	+		+	+	+	+		+	8/10
Interleukin 8 produced by tumour cells	+	+	+	+	+	+	+		+		8/10
Increased serum concentrations of interleukin 6	+	+	+	+	+	+		+	+	+	9/10
Decreased expression of interleukin 12			+	+	+		+	+	+	+	7/10
Decreased interferon-γ production in immune cells	+		+	+	+		+		+	+	7/10
Reduced expression of HLA-DR	+		+		+	+	+			+	6/10
Increased serum concentrations of transforming growth factor-β	+	+	+	+			+	+	+		7/10
C-X-C motif chemokine receptor 4 tumour expression	+	+	+	+	+	+	+	+	+		9/10
Increased serum concentrations of interleukin 10	+	+	+	+	+	+	+	+			8/10

Lancet 2013, 14:e218-228

Published evidence for specific cytokine effects in various cancer types

	Lung	Breast	Colo rectal	Gastric	Malignant melanoma	Oesophageal	Pancreatic	Hepato cellular carcinoma	Renal cell	Diffuse B-cell lymphoma	
Macrophage migration inhibitory factor expression and negative prognostic effect	+	+		+		+		+			5/10
Interleukin 8 is associated with tumour size, depth of infiltration, or increased stage	+	+	+	+		+		+		+	7/10
Interleukin-6 serum concentration and negative prognostic effect	+	+	+	+	+	+	+		+	+	9/10
Interleukin-18 serum concentration associated with advanced stage	+	+				+		+	+		5/10
Increased interleukin-18 serum concentration and negative prognosis	+			+			+	+		+	5/10
High expression of HLA-DR and positive prognosis	+	+	+		(+) serum soluble HLA-DR		+	(+) downregulated genes		+	7/10
C-X-C motif chemokine receptor 4 tumour expression associated with metastases	+	+	+	+	+	+	+	+	+		9/10
Raised interleukin-10 serum concentration associated with a negative prognostic effect	+		+	+	+		+	+	+	+	8/10

Lancet 2013, 14:e218-228

Interferon-Alpha 2b

- Anti-Viral
- Immune stimulation
- MHC gene expression
- Type I and II interferons

Interferon-Alpha 2b: Renal cancer

- Optimal therapeutic dose: 5 to 10 MU/m^2 for 3 to 5 days SQ.
- Cochrane meta-analysis: Included four studies involving a total of 644 patients.
  - Treatment with IFNa was superior to controls - odds ratio for death at one year 0.56, 95% CI 0.40-0.77
  - overall hazard ratio for death 0.74, 95% CI 0.63-0.88).
  - The weighted average median improvement in survival was 3.8 months.

- IFNa plus bevacizumab is an approved and active regimen.
  - Data Unclear but promising.

Cochrane database 2005: Immunotherapy for advanced renal cell cancer

Interferon-Alpha 2b: Melanoma

Study	Stage	No. of Patients	Treatment	Median Follow-Up (years)	Impact on PFS		Impact on OS		Toxicity Attrition Rate (%)	Note
					HR	P	HR	P		
ECOG E1684[2]	T4, N	287	IFN-α2b 20 MU/m^2 per day IV for 1 month followed by 10 MU/m^{2}SC three times per week for 11 monthsvobservation	6.9	0.61	0.001	0.67	0.01	26	At 12.6 years, the impact of competing causes of death on OS cannot be ignored
				12.6	0.72	0.02	0.82	0.18		
ECOG E1690[3]	T4, N	642	IFN-α2b 20 MU/m^2 per day IV for 1 month followed by 10 MU/m^{2}SC three times per week for 11 monthsv 3 MU per day given SC three times per week for 2 years vobservation	4.3	0.78	0.05	1		13	Cross-over of patients from observation to high-dose IFN-α2b at nodal relapse (n = 38) is expected to affect OS analysis
				6.6	0.81	0.09	1			
ECOG E1694[4]	T4, N	880	IFN-α2b 20 MU/m^2 per day IV for 1 month followed by 10 MU/m^{2}SC three times per week for 11 monthsv GMK vaccine for 96 weeks	1.3	0.67	< .001	0.72	0.023	10	
				2.1	0.75	0.006	0.76	0.04		
EORTC 18991[9]	Tx, N	1,256	PEG IFN-α2b given SC at 6 μg/kg per week (for 8 weeks) followed by 3 μg/kg per week (for 5 years) vobservation	3.8	0.82	0.011	0.98		37	
				7.6	0.87	0.055	0.96			

Journal of Clinical Oncology 2012, 30: 3773-76

IL-2: Renal cancer

- In seven phase II studies, recombinant IL-2 (600,000 to 720,000 international units per kg) was administered as a 15 minute intravenous (IV) infusion every eight hours over five consecutive days (up to 14 consecutive doses).
- Toxicities: Severe (hypotension, arrhythmia, acidosis, fever, nausea)

- Outcomes Case Study 1989-2005:
  - Patients with metastatic disease receiving immunotherapy (**n=453**)
  - complete response in 7% (median survival [MS], 120+ months),
  - partial response in 15% (MS, 42.8 months),
  - stable disease in 33% (MS, 38.6 months), and
  - progressive disease in 45% (MS, 11.6 months).

Cancer. 2008;113(9):2457-63

IL-2: Melanoma

- IL-2 is a form of immunotherapy that was found to help some people with metastatic melanoma when given in high doses. In some people treated with high-dose IL-2, the disease disappeared completely or stopped growing for a prolonged period.

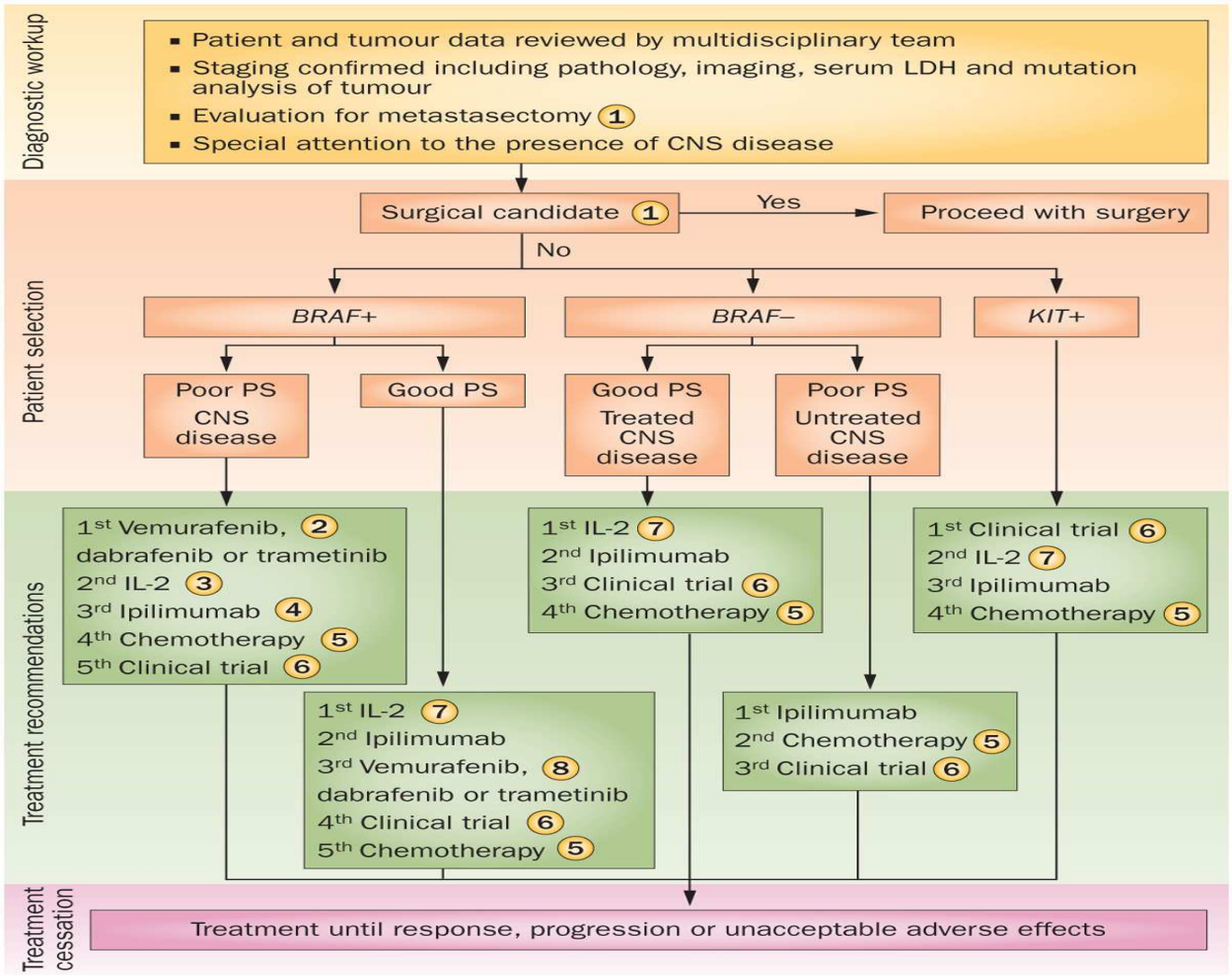
- Treatment usually required being in the hospital.

- IL-2 has largely been replaced by checkpoint inhibitors, which are safer and more effective.

- BAY50-4798: modified IL-2

SITC Statement: Stage IV melanoma immunotherapy treatment algorithm

Nat. Rev. Clin. Oncol. 2013, 10:588-98



Granulocyte Monocyte Colony Stimulating Factor

- Approved for use in stem cell and bone marrow transplant to reconstitute the myeloid series.
- GM-CSF has ben around for 41 years, yet limited data!!!
- Melanoma trial, monotherapy n=48 with stage III and IV melanoma
  - treated with long-term, chronic, intermittent GM-CSF after surgical resection.
  - Overall and disease-free survival were significantly prolonged by GM-CSF therapy in patients who were clinically disease-free. Median survival was 37.5 months versus 12.2 months in matched controls ($P < 0.001$).
  - Treatment was well tolerated.

IL-12

- Monotherapy with IL-12 - minimal therapeutic potential.
- Modest antitumor activity in metastatic renal cell carcinoma and melanoma.
- GM-CSF and IL-12 – highly unlikely to stand alone

Future directions

- Adjuvant therapy with chemo and vaccine therapy
- More research in combination with JAK/STAT and other transcription factor inhibitors
- Combination with immune check point inhibitors.