Regular Review

Interferon for treatment: the dust settles

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The first clinical trial of leucocyte interferon began in 1972 at the Karolinska Institute when it was used to treat osteosarcoma.[1] Other malignancies were also treated, and expectations ran high that this new "biological response modifier" would be a breakthrough in cancer treatment. The drug's efficacy was, however, overstated. In the words of one of the first people to use interferon: "Much second class research was carried out with third class preparations slightly contaminated with interferon."[2]

Highly pure interferon can now be produced on a large scale, but clinical trials of interferon for both malignancy and viral infection have been disappointing. Fifteen years after it was first used in treatment interferon alfa has four licensed indications—hairy cell leukaemia, chronic granulocytic leukaemia, Kaposi's sarcoma, and condylomata acuminata.[3]

Types of interferon

All types of interferon have one thing in common—antiviral activity that works by inhibiting production of viral RNA and protein.[4] This "interference" led to the term "interferon" and allows the measurement of the biological activity of interferon preparations in terms of "antiviral units." Cultured monolayers of cells are infected with a standardised dose of virus, which then destroys them; inhibition of this process by the interferon present allows accurate quantification. (Immunoradiometric methods of measuring interferon using monoclonal antibodies are also now available.)

Three types of interferon are recognised—alfa, beta, and gamma. Interferon alfa and interferon beta have similar characteristics—for example, they share the same cell surface receptor—but interferon gamma is a different molecule with stronger immunomodulatory effects.[5]

Interferon alfa was the first interferon to become available on a large scale, when Cantell extracted it from buffy coats at the Finnish blood transfusion service. This product was only 1% pure and contained other lymphokines, which makes it difficult to interpret the results of clinical trials that used the product. Over 30 subtypes of interferon alfa have been identified, the most biologically important being interferon alfa-2.

Interferon alfa that is more than 99% pure can be produced by two different techniques. Firstly, a human lymphoblastoid cell line can be stimulated in vitro to produce a combination of interferon alfa subtypes, which are then purified by chromatography (Wellferon, Wellcome).[6] Secondly, recombinant molecular technology has led to the insertion of human DNA sequences coding for interferon alfa-2 into *Escherichia coli*, which then express large quantities of the molecule, which is again purified by chromatography (Roferon, interferon alfa-2a, Roche; Intron, interferon alfa-2b, Schering).[7] It is not clear which, if any, of the three commercially available products is clinically superior.

Actions of interferon

Interferon has direct effects on cell metabolism as well as indirect effects through the immune system. Both effects result from interferon molecules binding to their cell surface receptors which trigger intracellular signals that regulate gene transcription, translation, or both.[8]

The best understood direct action of interferon is the production of the enzyme 2'5'A synthetase by the stimulated cell (the stimulus may be a virus, an antigen, or interferon itself).[9] This enzyme breaks down viral RNA through an endonuclease, thus inhibiting viral replication. It is not clear whether this system has any influence in interferon's antiproliferative effect on cells that are not infected with viruses, but several other enzyme systems may be stimulated to inhibit cell proliferation or promote differentiation.[10] Direct actions of interferon on oncogene expression have also been described and may give an insight into the regulation of tumour growth.[11]

Interferons stimulate the immune system to combat many assaults. They enhance the cytotoxicity of T lymphocytes and natural killer cells; regulate immunoglobulin synthesis; stimulate macrophage participation in T cell cytotoxicity; and increase phagocytosis by monocytes and neutrophils.[12]

Pharmacological properties

Only interferon alfa has been available in large enough quantities for clinical use, although some small trials of recombinant interferon gamma have been performed. Although chiefly an antiviral agent, interferon has not been useful in acute viral infections but may have a place in treating some chronic viral infections. The greatest success has been in treating haematological malignancies.

Phase one clinical trials showed that high dose intravenous interferon alfa had little benefit.[13] Lower doses given

subcutaneously are better tolerated. Half of patients cannot tolerate more than 20 megaunits daily because of toxicity[14]; consequently most doctors use 3 megaunits daily as initial treatment reducing the frequency for maintenance. Peak serum concentrations of interferon alfa are achieved around six hours after subcutaneous injection,[15] and the serum half life is between six and 12 hours; interferon alfa is thus given in the early evening so that the maximal side effects coincide with sleep.

Features of the interferons

Characteristic	Interferon alfa	Interferon beta	Interferon gamma
Synonym	Leukocyte	Fibroblast	Immune
Subtypes	Over 30	Beta-1 (beta-2)	No subtypes
Molecular weight	20 kd	26 kd	17 kd
Cell of origin	Monocyte/ macrophage	Fibroblast/ macrophage	T lymphocyte
Main inducing stimuli	Virus	Virus	Antigen/mitogen
Effect on human leukocyte antigen expression	Weak	Weak	Strong

Side effects were initially thought to be caused by impurities, but toxicity also occurs with highly purified products. Both interferon alfa and interferon gamma have a similar range of toxicity. Typically fever and an influenza like syndrome occur on starting treatment but improve over the next few weeks. Younger patients tolerate the symptoms better than the elderly. Fatigue is the most common problem[14] and may be a direct effect of interferon alfa on the nervous system. More profound psychomotor retardation or progression to unconsciousness is rare. Nausea and anorexia may occur and result in a loss of weight that requires monitoring. Blood activities of hepatic transaminases must also be checked regularly, as a third of patients have raised activities initially.

Interferon alfa suppresses all blood cell precursors in the bone marrow, resulting in cytopenias or anaemia.[16] This may be a direct effect or may result from increased natural killer cell activity. Alternatively, cytopenias may result from a redistribution of circulating blood elements.[17] Thrombocytopenia is the most troublesome problem in patients with haematological malignancies.

Initial side effects are best controlled by giving paracetamol or metoclopramide and by giving the interferon in the evening. After a few weeks side effects usually abate; otherwise dose reduction or temporary interruption of treatment may be tried.

Interferon alfa in malignancy

The chronic leukaemias have been most responsive to interferon alfa, in particular hairy cell leukaemia, which has a response rate of 90%. Hairy cells are usually eradicated from the peripheral blood, but the bone marrow returns to normal in only one quarter of responders.[3,18] Interferon alfa is started for the progressive cytopenias typical of hairy cell leukaemia, but it is not yet clear whether interferon alfa will replace splenectomy as the primary treatment.[19] As circulating leukaemic cells disappear the other peripheral blood elements return towards normal. Treatment is started at 3 megaunits daily, but this is reduced to thrice weekly once control is achieved. A six month course of interferon alfa is usual, but patients must be observed closely after treatment is stopped. Those who relapse often respond well when treatment is restarted.[20] As hairy cell leukaemia has a long natural course we do not yet know whether interferon alfa improves survival.

Cells containing the Philadelphia chromosome, which are typical of chronic granulocytic leukaemia, may be suppressed by interferon alfa and may be abolished in some patients.[21] (This does not happen with the standard busulphan treatment.) This effect has been sustained in some patients, but it is not clear whether interferon reduces acute transformation or prolongs survival.

Multiple myeloma[22] and low grade non-Hodgkin's lymphoma[23] are not sufficiently responsive to interferon alfa for it to be used as primary treatment, but there is growing evidence that interferon alfa may be a suitable adjunct to maintenance treatment in delaying the progression of these disorders.[24] Although chronic lymphatic leukaemia is allied to non-Hodgkin's lymphoma, it does not respond well to interferon alfa.[25]

Kaposi's sarcoma responds in around two fifths of patients given interferon alfa, but relapse is common when treatment is stopped.[26] Interestingly, those who respond (all of whom are infected with the human immunodeficiency virus (HIV)) have less opportunistic infections than non-responders; this probably reflects the patient's disease pattern rather than a protective effect of interferon alfa.[27]

Several studies of treating malignant melanoma[28] and renal cell carcinoma[29] with interferon alfa have reported the occasional dramatic response, but the overall response rates are generally between 10% and 20%. Interferon alfa may potentiate the cytotoxicity of other chemotherapies, but this has not been tried in these conditions.[30]

The responses to interferon of the rare hormone secreting pancreatic neoplasms and carcinoid tumours have proved interesting.[31,32] In both there is often advanced metastatic disease unresponsive to standard chemotherapies, but interferon alfa may reduce hormone secretion and symptoms in these advanced cases.

The common malignancies (breast, lung, prostate, colon, and ovary) and acute leukaemia respond poorly to interferon alfa. Some common benign neoplasms associated with human papillomavirus infection (condylomata acuminata,[33] uterine cervical dysplasia,[34] and juvenile laryngeal papillomatosis[35]) have responded well to interferon alfa. Juvenile laryngeal papillomatosis is a distressing cause of laryngeal obstruction in children and responds in most patients treated with interferon alfa, but relapse is common when treatment is stopped. Interferon alfa has not been popular treatment for the other two conditions, presumably because less expensive alternatives are effective.

Interferon alfa in viral disorders

Healthy people produce enough endogenous interferon to cope with acute viral infections; patients with immunodeficiency cope less well. Thus exogenous interferon is not useful in acute viral infections except for prophylaxis. When given intranasally it reduces the risk of rhinovirus infection, but as epistaxis is a hazard of treatment it is best reserved for immunodeficient patients.[36] Interferon alfa does not reduce the infection rate by much in patients immunocompromised by HIV infection.[37]

Patients with hepatitis B[38] or non-A, non-B hepatitis[39]

respond to interferon alfa with a reduction in serum transaminase activities and in markers of viral activity. Occasionally the virus is eradicated from within the hepatocyte, but more commonly the virus and hepatic disturbance reappear when treatment is stopped. It is not clear what effects interferon alfa has on the development of associated chronic hepatitis.

Interferon gamma treatment

A few phase one clinical trials of using interferon gamma to treat various malignancies have taken place in the United States.[40] Except for a suggestion of antitumour activity in lymphoproliferative disorders,[41] there are no disorders particularly susceptible to interferon gamma.

Future trends

The therapeutic use of the interferons as single agents is unlikely to be expanded by much, but they may be useful in combination with other antitumour drugs. Research on interferons has, however, given much impetus to exploring treatment with other "biological response modifiers"—for example, interleukin 2, colony stimulating factors, and so on.

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