Interferon, Interleukin-2, and Other Cytokines

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KEYWORDS

• Melanoma • Cytokines • Interferon • Interleukin-2 • Interleukin-21
• Granulocyte-macrophage colony–stimulating factor

KEY POINTS

- Interferon-α has immune-modulating effects and when used at high dosages in the adjuvant setting has an impact in preventing recurrence in high-risk melanoma patients.
- Interleukin-2 plays a complex role in the immune system and when given at high dosages to patients with metastatic melanoma a subset achieve a long-term durable complete response.
- The use of cytokines in the treatment of melanoma continues to evolve as does their role in combination with other immune-modulating agents and targeted therapies in the future of melanoma treatment.

CYTOKINES

Cytokines are a complex group of naturally occurring glycoproteins produced when the immune system is activated by an infection, foreign antigen, or self-antigen. The antitumor effects of cytokines are likely mediated through immunomodulation, antiproliferative activity, and inhibition of angiogenesis. Melanoma has proved to be one of the most immunogenic malignancies based on documented cases of spontaneous regression and its higher prevalence in immunocompromised patients. This evidence of immunogenicity has led to the testing of numerous cytokines including interferon (IFN)-α, IFN-γ, granulocyte-macrophage colony–stimulating factor (GM-CSF), interleukin (IL)-2, IL-4, IL-6, IL-12, IL-18, and IL-21 in patients with advanced melanoma.

INTERFERON

In 1957 Isaacs and Lindenmann[1] were studying the influenza virus and discovered that incubation of heated virus with chick chorioallantoic membrane led to release

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of a previously unknown factor. This factor interfered with growth of live virus in fresh pieces of membrane and was named "interferon." In parallel, Yasuichi Nagano was discovering IFN while exploring antiviral activity that occurred after injecting inactivated vaccinia virus into rabbit skin.[2]

Subsequently, IFNs were found to be produced in many animal cells and tissues. Ten mammalian IFN species have been discovered. Of these eight are found in humans, six are type I (IFN-α, IFN-β, IFN-ε, IFN-κ, IFN-ω, and IFN-ν), one is type II (IFN-γ), and one is type III (IFN-λ).[3,4] IFN was purified from human fibroblasts and the mRNAs responsible for its production were isolated.[5,6] A full length copy of the IFN sequence was found leading to the ability to produce and purify a recombinant IFN-α2 that expanded opportunities for its use in research and clinical trials.

The actions of IFNs are mediated by interaction with the receptors IFNAR1 and IFNAR2.[7] These receptors are multichain complexes that use several signaling pathways within the cells. One of the pathways activated through the action of IFN is the JAK-STAT pathway.[8]

Treatment with IFNα2b has numerous effects on the immune system. It leads to the downregulation of intercellular adhesion molecule and the upregulation of HLA-DR expression, which may modulate tumor cell-host immune response. In addition natural killer cell function, T-cell function, and subset distribution are modulated in patients treated with IFN.[9] In addition it can lead to the induction and/or activation of proapoptotic genes and proteins, such as TRAIL, caspases, Bak, and Bax, and repression of antiapoptotic genes, such as Bcl-2 and IAP.[10]

IFN-α has multiple effects in a variety of malignancies and has been the most broadly evaluated clinically. There are three commercially available isoforms that differ by one to two amino acids: IFN-α2a (Roche), IFN-α2b (Merck), and IFN-α2c (Boehringer Ingelheim). IFN has been approved for the treatment of hairy cell leukemia, relapsing-remitting multiple sclerosis, malignant melanoma, follicular lymphoma, condylomata acuminate (genital warts), AIDS-related Kaposi sarcoma, and chronic hepatitis B and C.

Initial Use in Melanoma

As with all antineoplastics the first testing of IFNs in melanoma was in the metastatic disease setting. In 1978, the American Cancer Society initiated a multicenter trial testing IFN-α in patients with metastatic melanoma. Forty-five patients were enrolled among whom there was one partial responder and minimal responses in two others.[11,12] A similar study was performed by Retsas and colleagues[13] in which 17 patients with melanoma were treated with IFN-α and one partial response was seen.

Studies continued as more dosing information became available. Several phase I/II studies were performed with very similar results. In these trials there were 2 responses out of 15 patients, 4 responses out of 23 patients, and 3 responses out of 20 patients.[12] Tumor response rates around 16% were observed with some late responders. It is unknown if there is a survival benefit for IFN in the metastatic setting because no randomized trials comparing it with cytotoxic therapy or supportive care have been performed. Most of the responders had a low tumor volume.[14] This led to the hypothesis that the greatest benefit of IFN-α would be in patients with microscopic residual disease.

Adjuvant Testing

Randomized phase III trials have been performed testing both high-dose IFN-α2b and pegylated (PEG) IFN-α2b in the adjuvant setting in high-risk melanoma patients (**Table 1**). The first trial was Eastern Cooperative Group E1684, a randomized