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AIDS-ASSOCIATED KAPOSI'S SARCOMA: IS THERE STILL A ROLE FOR INTERFERON ALFA?

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Abstract

Interferon alfa (IFNA) was one of the first agents to be used therapeutically in AIDS-associated Kaposi's sarcoma (KS) more than 25 years ago, and induces tumor regression in a subset of patients. Although much has been learned about the clinical role of IFNα in KS treatment, little is currently known about the mechanism(s) by which IFNA causes KS regression. This is despite a growing understanding of both KS pathogenesis and relevant IFNA activities. To a large extent other agents have supplanted IFNA as treatments for KS, but there may still remain a therapeutic role for IFNA, possibly in combination with other agents targeting angiogenesis and/or HHV-8-encoded human gene homologs that encode proteins involved in cell cycle regulation and signaling.

Keywords

Interferon; Kaposi's sarcoma

In 1995, when I was honored as a recipient of the ISICR Milstein Award, the AIDS epidemic had recently begun its 15th year and the human immunodeficiency virus (HIV-1) had been isolated some 12 years previously [1]. However, the virus associated with Kaposi's sarcoma (KS), the most common AIDS-associated malignancy, had been described less than a year earlier [2], its significance was still in some question and its role in KS development had not been characterized, and the active combination drug regimens with which we now treat HIV infection had not yet become widely available. Recombinant interferon alfa preparations (IFNα2a and IFNα2b), which had received approval from the U.S. Food and Drug Administration (FDA) for treatment of AIDS-associated KS in 1988, were still the *only* approved drugs for systemic treatment of KS (the chemotherapeutic agent, liposomal doxorubicin, would receive FDA approval later in 1995, as did liposomal daunorubicin in 1996 and paclitaxel in 1997).

Now, more than a quarter century after the first published reports describing AIDS and its association with KS [3–6] and our first modestly successful attempts to treat KS with IFNα [7], this agent is used infrequently to treat KS, although it still finds use in HIV-infected individuals co-infected with hepatitis C. In this brief review, I will summarize some of the history of IFNα in the treatment of AIDS-associated KS, concentrating on examples of clinical trials in which I have personally been involved, and consider whether there remains a potentially valuable role for this agent in KS treatment.

1. IFNα as single agent therapy – a requirement for high IFN doses

My colleagues and I treated our initial group of patients with AIDS-associated KS with recombinant IFNα2a in late 1981 and early 1982 during the course of one of the first phase I clinical trials of this agent in cancer patients. This trial, which involved the administration of escalating doses of IFNα2a to successive patient cohorts, had as its primary aim the evaluation of the safety, toxicity and maximum tolerated dose of this agent in a diverse group of cancer patients, and as a secondary aim to seek evidence for anticancer effects. So it was entirely by chance that these initial KS patients were treated at a time when study subjects were being given IFN at doses near the maximum tolerated dose. Of the first 12 such patients whose response to treatment could be evaluated, 5 (42%) showed complete or partial (≥50 %<100%) KS regression and 3 others showed minor responses [7]. At the time, relatively little was known about the mechanisms of IFNα's action against cancer, and even less about the nature or cause of KS. Admittedly, given the high general level of enthusiasm for IFN at that time, one did not need to invoke an elaborate rationale to justify studying IFN in any sort of cancer. Nonetheless, we believed that an agent with antiproliferative, immunomodulatory and antiviral activities might be a particularly appropriate candidate for evaluation in a neoplasm that was associated with immunodeficiency and in which cytomegalovirus had been implicated as a potential etiologic factor (wrong herpesvirus, right idea) [8,9]. In subsequent clinical trials in larger numbers of patients we confirmed that high-dose IFNα was active against KS, whereas the administration of lower, better tolerated IFN doses rarely induced KS regression [10]. The apparent dose-dependency of the KS response was interpreted by some to indicate that IFNα acted directly on tumor cells, and that its action was mainly antiproliferative.

1.1 Correlates of Response

Additional attempts to understand IFN's mechanism of action were limited to studies of pre-treatment correlates of response. We showed that a history of opportunistic infections (a clinical indicator of more severely impaired immune function), but not the extent of the KS lesions, was associated with a low response of KS to high-dose IFNα treatment [10,11]. These observations were consistent with our finding that blood tests indicative of more preserved immune function (ie, higher CD4+ T-cell counts, higher *in vitro* lymphocyte proliferative responses to microbial antigens) and the absence of evidence for activation of the endogenous IFN system (measured by the presence of circulating IFNα and elevated levels of the IFN-inducible products, neopterin and beta$_2$-microglobulin) were strongly associated with responsiveness of KS to IFNα2a treatment [11].

2. IFNα combined with first-generation antiretroviral therapy – lower IFN doses are active

The FDA approval of the nucleoside reverse transcriptase inhibitor zidovudine (ZDV; known also as azidothymidine, or AZT) for treatment of HIV infection in 1987, and the demonstration that the combination of ZDV and IFNα synergistically inhibited HIV replication *in vitro* [12], led logically to studies of this combination in HIV-infected individuals, including those with KS. Our phase I trial of the combination showed that the addition of ZDV resulted in a decrease in the maximum tolerated dose of IFN, largely because of the development of neutropenia [13]. Nonetheless, the response rate of KS to the combination was higher than we had observed previously using IFN alone. In addition, while patients with higher baseline CD4+ T-cell counts still showed the highest response rates, those patients whose baseline CD4+ T-cell counts were low (<200/μL) at study entry responded more frequently to the combination than had been observed when similar patients had been treated with higher doses of IFN as a single agent [13]. The increased development of hematologic toxicity with the combination was not surprising, as we had shown synergistic inhibition of bone marrow myeloid and erythroid

progenitor cell growth *in vitro* when IFN and ZDV were combined [14]. Although we were able to prevent neutropenia by the addition of GM-CSF to the IFN and ZDV combination, non-hematologic toxicity prevented an increase in the IFN dose [15].

The reasons for the superior activity of the IFN and ZDV combination against KS were not clear, however. Although this combination had been shown to synergistically suppress plasma HIV p24 antigen levels in vivo in HIV-infected individuals [16], a randomized community-based trial that compared the combination of IFN and ZDV to ZDV alone in asymptomatic or minimally symptomatic HIV-infected adults without an AIDS-defining illness demonstrated no superiority for the combination with respect to clinical endpoints, CD4 counts, or the development of ZDV resistance, and the tolerance of treatment was inferior in the combination therapy arm [17]. Thus, while lower IFN doses with ZDV appeared superior to high-dose IFN alone in inducing regression of KS, and some KS patients with advanced CD4+ T-cell immunodeficiency were now able to benefit from treatment, we were no closer than before to understanding the mechanism of the anti-tumor effect.

3. Is less IFN more?

Our early experiences strongly suggested that optimal KS responses to IFNα required that we use the highest doses that could be administered without causing unacceptable toxicity. However, the realization that lower doses could be active in combination with antiretroviral therapy, as well as a desire to minimize the significant toxicities sometimes associated with high-dose treatment, led us to evaluate the combination of lower doses of IFNα with didanosine, a nucleoside reverse transcriptase inhibitor with less myelosuppressive activity than ZDV. Whereas in previous studies of IFNα as a single agent, daily doses of 30 million international units (IU) or more were required to achieve KS regression, and doses of 4.5 to 18 million IU were tolerated in combination with different ZDV doses, we designed a randomized trial that compared the tolerance and antitumor efficacy of daily IFNα doses of 1 million and 10 million IU with didanosine [18]. Although a non-significantly higher response rate was observed among patients who received the higher IFN dose, any advantages attributable to higher-dose IFN were offset by its significantly poorer tolerance, resulting in a higher rate of treatment discontinuation and dosage attenuation among patients randomized to the higher-dose treatment arm, and there were no significant differences in survival between the treatment groups [18]. In addition, CD4+ T-cell counts increased during treatment at a higher rate among patients in the low-dose arm. As with the previous studies, the CD4+ T-cell count at baseline correlated with treatment response.

4. Developing a better understanding of KS pathogenesis

KS has long been described as an “angiogenic” neoplasm, in the sense that a characteristic histologic feature is the proliferation of endothelial cell-lined slit-like vascular spaces. Recent gene expression profiling analyses have shown that spindle cells, which form the major cellular component of the lesions, most closely resemble lymphatic endothelium [19]. The lesions also contain a variable inflammatory and mononuclear cell infiltrate. Studies published beginning in the late 1980s indicated that spindle cells derived from KS lesions could release, proliferate, and/or migrate in response to various growth factors that stimulate angiogenesis, including vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), interleukins -1, -6 and -8, and platelet-derived growth factor (PDGF), and over-express receptors for multiple cytokines [19–22]. Activation of these receptors stimulates multiple pro-growth and anti-apoptotic pathways via PI3kinase/Akt/mTOR and extracellular receptor kinase (ERK) [23]. Pertinently, biopsies of KS tissue have been shown by immunohistochemistry to express elevated levels of phosphorylated Akt, p70 S6 kinase, PDGF-receptor (PDGFR) and ERK [23,24]. These observations and others have formed the rationale for small clinical trials of

imatinib (which inhibits both PDGFR and c-kit) and rapamycin (which inhibits phosphorylation/activation of the p70 S6 kinase downstream of mTOR); early suggestions of antitumor efficacy have been observed in these trials [23,24]. KS cells also over-express matrix metalloproteinases (MMPs) [25], enzymes involved in the destruction of extracellular matrix proteins during angiogenesis and metastasis, and express high levels of the vitronectin receptor $\alpha_v\beta_3$, a vascular integrin that is strongly up-regulated on activated endothelium [26].

4.1 The role of HHV-8

It was not, however, until December, 1994 that the existence of a newly-described virus, human herpesvirus 8 (HHV-8, also known as the Kaposi's sarcoma-associated herpesvirus, KSHV) was first reported [2]. Subsequent studies of HHV-8 gene expression have provided insights into potential mechanisms by which the virus may induce angiogenesis and KS lesion development. The HHV-8 viral genome is noteworthy for the presence of a large number of human gene homologs that encode proteins involved in cell cycle regulation and signaling. These include genes expressed during viral latency (LANA-1, a viral cyclin homolog and vFLIP) that act variously to inhibit apoptosis and prevent cell-cycle arrest by pRB [27–29], and additional gene products transcribed during lytic replication corresponding to cellular proteins involved in cell cycle progression, apoptosis, proliferation and immune regulation. These include the K1 protein, a viral BCL-2 homolog, a viral GPCR, a viral homolog of IL-6, viral macrophage inflammatory proteins vMIPs, and several viral interferon regulatory factors [30–34]. Notably, mice transfected with the vGPCR develop vascular tumors resembling KS [35], which suggests a key role for this gene product in KS development. Additionally, cells transfected with the vGPCR or K1 secrete vascular endothelial growth factor (VEGF) [34, 38], which is overexpressed in KS lesions [36] and activate the VEGF-R2 [37]. The vGPCR and K1 also activate NFκB, which induces transcription of various angiogenic and pro-inflammatory mediators including VEGF and MMP-9 [30,32,33,38]. The HHV-8 genome contains coding sequences for four IRF homologs, vIRFs 1–4. vIRF3/LANA-2 is expressed during latency in primary effusion lymphoma cell lines, but is virtually undetectable in KS cells [39], so is unlikely to be of importance in regulating the response to IFN in KS. vIRF-1/K9, on the other hand, has been shown to interfere with IFN signaling [40,41] and can be detected in some KS lesions. It may be of some importance in regulating the differential response to IFN in KS [42]. Many of the proteins encoded by HHV-8 may also inhibit immune responses to the virus. For example, vFLIP blocks cytotoxic T-cell killing of HHV-8-infected cells by inhibiting Fas activation [43]; vMIP-II may restrict recruitment of Th1 lymphocytes to HHV-8-infected cells [44]; K1 may prevent class 2 MHC-mediated T cell activation by HHV-8 [45]; and K3 and K5 block cell surface display of class 1 MHC molecules on the cell surface [46]. Although the majority of cells within KS lesions show latent infection, a small subset expresses lytic cycle genes [47] and produce viral progeny [48].

5. IFN activities in the context of KS pathogenesis

A strong and specific rationale for treating AIDS-associated KS with IFN has accumulated over the past 25 years. This can be divided, broadly, into antiviral and angiogenesis-inhibitory activities of IFN, as follows.

5.1 Antiviral activities

Unlike most human tumors in which IFN has shown therapeutic activity, AIDS-associated KS is associated with two viruses, HHV-8 and HIV, each of which contributes to the development and severity of the lesions. HIV's effect on KS development and progression is indirect; it may contribute to the severity of the tumor by reducing the immune response to HHV-8, by stimulating the production of inflammatory cytokines, and by the release of its transactivator protein Tat, which acts synergistically with other angiogenic cytokines to stimulate spindle

cell proliferation, adhesion and migration *in vitro* [49]. Although multiple studies attest to the inhibitory effect of IFNα on HIV replication and its synergistic inhibitory activity in combination with other antiretroviral agents *in vitro* [12,50–52], it is not known to what extent (if any) inhibition of HIV contributes to IFN-induced KS regression.

Like HIV, HHV-8 replication has also been reported to be inhibited by IFNα *in vitro* when used alone or in combination with other antiviral agents [53–56], and IFNα has been shown to inhibit HHV-8 K1 gene expression in TPA-induced BCBL-1 and butyrate-induced BC-1 cells [53]. Again, the extent to which these antiviral activities may account for any of the effects of IFN on KS in patients is questionable. Although little data exists that directly addresses this point, in a recently reported study of the combination of IFNα2b with HIV protease inhibitor-based antiretroviral therapy, we performed serial measurements of HHV-8 viral load in 5 patients, including 2 whose KS regressed, 2 with stable KS, and 1 who showed progressive KS. None of these patients, irrespective of their KS response, showed durable clearance of KSHV from plasma or peripheral blood mononuclear cells during treatment [57].

5.2 Angiogenesis inhibition

Apart from its effects on the viruses implicated in AIDS-associated KS, IFNα has long been known to affect angiogenesis, a distinguishing feature of KS lesions. As early as 1980, IFN had been shown to inhibit endothelial cell motility [58], and later in the 1980s was shown to inhibit tumor- and allogeneic lymphocyte-induced angiogenesis [59] and to selectively damage the tumor microvascular endothelium, leading to coagulation necrosis of murine tumors selected for resistance to IFN's antiproliferative effects [60]. Further investigations of the angiogenesis inhibitory activities of IFN in the 1990s showed that IFNα could downregulate IL-8 production in fibroblasts [61] and bFGF in human tumor cell lines resistant to IFN's antiproliferative effects [62]. Building upon the latter observation in studies of human tumors implanted in nude mice, Fidler and colleagues showed that optimal inhibition of tumor weight, microvessel density, and expression of bFGF, MMP-9 and IL-8 were obtained when low, daily IFN doses were administered, whereas inferior effects were observed when isodense doses were given less often, or when higher IFN doses were used [63–65]. Observations made during the course of clinical trials in other diseases also attest to IFNα's ability to inhibit angiogenesis, and include regressions of highly vascular hemangiomas of infancy and pulmonary hemangiomatosis [66]. In addition, the response of highly vascular metastatic neuroendocrine tumors to IFNα was reported by von Marschall et al. [67] to be associated with both decreased microvessel density and VEGF mRNA in liver metastases that were biopsied before and during IFN treatment and with a decrease in plasma concentrations of VEGF. These observations were supported by *in vitro* studies showing that IFNα inhibited VEGF gene transcription through an Sp1- and/or Sp3-dependent inhibition of VEGF promoter activity [67].

In an editorial that accompanied the report by von Marschall et al. [67], Giovanna Tosato commented that, "IFN-α could be considered a broad-spectrum indirect angiogenesis inhibitor. As our understanding of the regulation of angiogenesis continues to improve, perhaps we will learn how best to use IFN-α as an anticancer agent that targets tumor angiogenesis [68]." These comments apply equally well to KS, a tumor that is particularly well suited to studies investigating the mechanism of action of angiogenesis inhibitors. The fact that KS almost invariably involves the skin distinguishes it from most other solid neoplasms because it is readily accessible to serial biopsies, whereas in most other solid cancers more invasive and potentially hazardous procedures (e.g., liver biopsy) are required. This is a distinct advantage if one wishes to directly investigate the mechanisms involved in tumor regression and use this information to optimize treatment. In fact, small lesional punch biopsies are currently being performed routinely as part of several clinical trials in KS, and are being used to evaluate the effects of various treatments on HHV-8 transcriptional profiles and expression of angiogenic

mediators. Unfortunately, tumor material was not systematically collected in past studies of IFN in KS. In those studies, post-treatment biopsies were usually obtained only to confirm the clinical impression of complete tumor regression, so any attempts to directly investigate IFN's effects on tumor cells would require new clinical trials with prospective collection of tumor tissue.

6. Barriers to the further development of IFN therapy for KS

Although there is clearly a strong and multifaceted rationale for its use, several factors have impeded the further development of IFNα for KS treatment.

6.1 Adverse effects

From a practical standpoint, the requirement for frequent self-injection has always been a disincentive to its use – patients find it unpleasant, if not worse. This, together with IFNα's well documented adverse effects (e.g., fever, flu-like symptoms, anorexia, cytopenias, liver function abnormalities), some of which may occur even during low-dose treatment, and the growing availability of alternative standard and investigational treatments for KS, have led to a reluctance to use IFN on the part of many patients and their physicians. Although a requirement for frequent self-injection could be lessened by the use of pegylated IFNs with much longer half-lives, optimal doses of these preparations have not been defined for KS and IFN-related toxicity is still an issue with the pegylated formulations.

6.2 Changes in KS incidence

Another major factor in IFN's decline as a treatment for KS has been the decreased incidence of this neoplasm among HIV-infected individuals in developed countries. Although this decline began before the widespread introduction of active combination antiretroviral therapy (collectively known as "HAART", or highly-active antiretroviral therapy) in 1996, an even greater decrease has occurred in the past decade [69], so fewer patients are available to participate in clinical trials. It should be noted that even among individuals with excellent suppression of HIV replication, new cases of KS are still diagnosed, progressive KS still occurs, and drug trials in KS are being conducted. However, the available number of patients does not currently permit the mounting of large clinical trials in KS without the cooperation of multiple institutions, and other agents have displaced IFN as a priority in multicenter clinical studies. It is also important to recognize that KS incidence is extremely high in sub-Saharan Africa [70–72] where HIV and KSHV infection rates are both much higher than in resource-rich parts of the world and where the availability of HIV treatments is limited. In such settings, however, the use of an injectable agent is impractical, although there remains a critical need for effective KS therapy.

6.3 Multiple potential mechanisms of action

An additional barrier to IFN's further development may, paradoxically, be the wide scope of its activities that might be relevant in the context of our understanding of KS pathogenesis. Unlike many agents recently investigated as potential KS treatments (e.g., the MMP inhibitor COL-3 [73], rapamycin [24] and imatinib [23]), which are purported to narrowly target proteins and signaling pathways that are over-expressed or activated in KS and are subject to focused analysis using serial sampling of blood or tumor tissue during the course of clinical trials, the multiplicity of IFN's potential mechanisms of action in KS is daunting. Most of the relatively large clinical trials of IFNα in KS were conducted well before the introduction of HAART, the discovery and characterization of KSHV, the elucidation of IFN's many potentially relevant activities and the technical capacity to study these as part of clinical trials. It is difficult to convince investigators and funding agencies to revisit an "old" drug when so many "new" agents are available.

7. The future for IFN in KS

For all these reasons, it is not highly likely that the studies that would be required to optimize the use of IFNα in KS, to clarify its mechanisms of action, and to identify the patients most likely to benefit, will be conducted. This is too bad, because in spite of the barriers limiting its use, IFNα has proven to be one of the more active agents in the treatment of KS, and has been shown to induce sustained and sometimes dramatic tumor regression in some patients even before the development of effective HIV therapy. There remains the possibility, however, that a role for IFN will be found in combination with some of the other pathogenesis-directed agents currently under investigation in KS. This possibility has been suggested by studies in another neoplasm, chronic myelogenous leukemia (CML), which like KS responds to treatment with both IFNα and imatinib. In a series of experiments in CML-derived cells, IFNα was shown to induce phosphorylation of mTOR and downstream phosphorylation of p70 S6 kinase, whereas imatinib induced the opposite effect on the mTOR/p70 S6 kinase pathway [74]. Nonetheless, both agents inhibited proliferation of leukemic progenitor cells, and this effect was enhanced by the addition of rapamycin to either IFNα or imatinib [74]. Although these seemingly paradoxical effects illustrate the difficulties involved in dissecting out the roles of different pathways involved in the many biological activities of IFN, they provide a possible rationale for similar investigations in KS.

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Biography

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