Direct Effects of Type I Interferons on Cells of the Immune System

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Abstract

Type I interferons (IFN-I) are well-known inducers of tumor cell apoptosis and antiangiogenesis via signaling through a common receptor interferon alpha receptor (IFNAR). IFNAR induces the Janus activated kinase–signal transducer and activation of transcription (JAK-STAT) pathway in most cells, along with other biochemical pathways that may differentially operate, depending on the responding cell subset, and jointly control a large collection of genes. IFNs-I were found to systemically activate natural killer (NK) cell activity. Recently, mouse experiments have shown that IFNs-I directly activate other cells of the immune system, such as antigen-presenting dendritic cells (DC) and CD4 and CD8 T cells. Signaling through the IFNAR in T cells is critical for the acquisition of effector functions. Cross-talk between IFNAR and the pathways turned on by other surface lymphocyte receptors has been described. Importantly, IFNs-I also increase antigen presentation of the tumor cells to be recognized by T lymphocytes. These IFN-driven immunostimulatory pathways offer opportunities to devise combinatorial immunotherapy strategies. Clin Cancer Res; 17(9); 2619–27. ©2011 AACR.

Background

Types of interferon

Interferons (IFN) were discovered in 1957 by Isaacs and Lindenmann as soluble proteins able to inhibit virus replication in cell cultures (1). There are 3 types of IFNs: type I (IFN-I), type II (IFN-II), and type III (IFN-III; refs. 2, 3). IFNs belonging to all IFN classes are very important for fighting viral infection. In humans, IFNs-I include IFN-α subtypes, IFN-β, IFN-ε, IFN-κ, and IFN-ω (2). From an immunologic perspective, IFN-α and IFN-β are the main IFN-I subtypes of interest. Both are produced by almost every cell of the body in response to viral infection and share important antiviral properties. The IFN-α family is a multitopic group of highly homologous polypeptides encoded by more than 13 intronless genes in humans. IFN-β, in contrast, exists as a single gene in most species. IFN-γ is the only IFN-II. This cytokine does not have marked structural homology with IFNs-I and binds a different cell-surface receptor (IFNγR), also composed of 2 different subunits (IFNγR1 and IFNγR2; ref. 2). The recently classified IFN-III consists of 3 IFN-λ molecules (IFN-λ1, IFN-λ2, and IFN-λ3) and signals through a receptor complex consisting of interleukin-10 receptor 2 subunit (IL-10R2) and IL-28 receptor alpha subunit (IL-28Rα; ref. 3). It is well established that IFNs induce the expression of hundreds of genes, which mediate various biological responses. Some of these genes are regulated by the 3 classes of IFNs, whereas others are selectively regulated by distinct IFNs.

Although the role of IFN-II and IFN-III is very important in immune responses, IFN-II has not yet shown any clinical activity for human cancer treatment (4), and IFN-III is not currently developed for any indication (3). However, since the discovery of IFNs, the use of IFN-I in therapy has been very widespread. In fact, systemic injections of IFN-I are approved for the treatment of a variety of diseases, which include solid and hematologic malignancies, multiple sclerosis, and, above all, chronic viral hepatitis. In this review, we focus on the role of IFN-I as a direct immunostimulatory agent directly modifying functions of immune system cells and how these functions can be applied to better therapeutic strategies.

IFN-I signaling pathways

All types of IFN-I signal through a unique heterodimeric receptor, interferon alpha receptor (IFNAR), composed of 2 subunits, IFNAR1 and IFNAR2, which are expressed in most tissues (5). IFNAR1 knockout mice have not only confirmed the role this subunit plays in mediating the biological response to IFNs-I, but have also established the pleiotropic role that these IFNs play in regulating the host response to viral infections and in adaptive immunity (6–8).

Receptor occupancy rapidly triggers several signaling cascades (Fig. 1), which culminate in the transcriptional regulation of hundreds of IFN-stimulated genes (ISG). The
first signaling pathway shown to be activated by IFNs-1 was the Janus activated kinase–signal transducer and activation of transcription (JAK-STAT) pathway (Fig. 1A; ref. 9), which is active in almost all cell types. IFNAR1 is constitutively associated with tyrosine kinase 2 (TYK2), whereas IFNAR2 is associated with JAK1. Receptor binding results in transphosphorylation of JAK1 and TYK2. The activated JAKs then phosphorylate conserved tyrosine residues in the cytoplasmic tails of the IFNAR. These phosphotyrosyl residues subsequently serve as docking sites for the recruitment of src-homology 2 (SH2)–containing signaling molecules, such as STAT1 and STAT2. Once at the receptor, the STAT proteins themselves become JAK substrates. STAT1 and STAT2 are both phosphorylated on a single tyrosine (Y701 for STAT1 and Y690 for STAT2). Once phosphorylated, STATs dimerize and move to the nucleus, where they bind specific GAS elements. C, PI3K and NF-κB pathways. Phosphorylation of TYK2 and JAK1 results in activation of PI3K and AKT, which in turn mediates downstream activation of mTOR, inactivation of GSK-3, CDKN1A, and CDKN1B, and activation of IKK, which results in activation of NF-κB. IFNs also activate NF-κB by an alternative pathway that involves the linkage of TRAFs, which results in activation of NF-κB. PI3K/AKT can also activate NF-κB through an activation loop via PKC. D, MAPK pathway. Activation of JAK results in tyrosine phosphorylation of Vav, which leads to the activation of several MAPKs such as p38, JNK, and ERK1/2. The different MAPKs activate different sets of transcription factors, such as Fos, ELK1, Sap-1, MEF2, MAPKAP, and Rok (activated by p38); Jun, ELK1, NFAT, and ATF2 (activated by JNK); and NFAT, ETS, ELK1, MEF2, STAT1/2, c-Myc, SAP-1, p33, SP1, and SMADs (activated by ERK1/2).
phosphorylation, activated STATs form homo- (STAT1, STAT3, STAT4, STAT5, and STAT6) or heterodimers (STAT1/2, STAT1/3, STAT1/4, STAT1/5, STAT2/3, and STAT5/6; refs. 10, 11, 18, 19), which translocate to the nucleus and bind other regulatory sequences known as IFN-γ–activated sites (GAS).

Interestingly, distinct STATs have opposing biological effects. Thus, STAT3 stimulates growth, whereas on the contrary, STAT1 is a growth inhibitor. On the other hand, IFNs-I–mediated activation of STAT4 is required for IFN-γ production, whereas surprisingly, STAT1 negatively regulates the IFNs-I–dependent induction of IFN-γ (20). The relative abundance of these dimeric transcription factors, which may vary substantially depending on cell type and activation and/or differentiation state, is likely to have a major impact on the overall response to IFNs-I (21–23).

Stimulation of the IFNAR/JAK/STAT1 pathway can also lead to the upregulation of the TAM receptor Axl, which accumulates at the cell surface where it physically associates with the IFNAR and usurps the IFNAR-STAT1 pathway by stimulating the transcription of suppressors of cytokine signaling (SOCS; refs. 24, 25). The SOCS proteins extinguish IFN-I signaling in a negative feedback loop. For instance, SOCS1 directly interacts with JAKs blocking their catalytic activity, whereas SOCS3 seems to inhibit JAKs after gaining access by receptor binding. In addition, SOCS proteins interact with the cellular ubiquitination machinery through the SOCS-box region and may redirect associated proteins, such as JAKs or IFNAR chains, to proteasomal degradation. It has been shown that SOCS1 knockout mice develop lupus-like disease symptoms (26) and that SOCS1 silencing enhances the antitumor activity of IFNs-I (27), suggesting that SOCS are key elements in keeping IFNs-I effects under control.

**Alternative signaling pathways and cross-talk with other receptors**

Evidence is accumulating that several other signaling elements and cascades are required for the generation of many of the responses to IFNs-I, such as the v-crk sarcoma virus CT10 oncogene homolog (avian)-like (CRKL) pathway, the mitogen activated protein kinase (MAPK) pathway, the phosphoinositide 3-kinase (PI3K) pathway, and either the classical or the alternative NF-κB cascade (Fig. 1B-D; refs. 9, 28). Some of these pathways operate independently of the JAK-STAT, whereas others cooperate with STATs to tune the response to IFNs-I. Interestingly, MAPK, PI3K, and NF-κB pathways involve immunoreceptor tyrosine-based activation motives used by classical immunoreceptors, suggesting a cross-talk among IFNAR and multiple receptors on immune system cells.

**The PI3K and NF-κB pathways.** Upon activation, TYK2 and JAK1 phosphorylate insulin receptor substrate 1 (IRS1) and 2 (IRS2), which provide docking sites for the PI3K (9). STAT3 acts as an adapter to couple PI3K to the IFNAR1 subunit. PI3K subsequently activates the serine-threonine kinase AKT, which in turn mediates downstream the activation of mTOR and the inactivation of several proteins, such as glycogen synthase kinase 3 (GSK-3) and cyclin dependent kinase inhibitors 1A and 1B (CDKN1A and CDKN1B), all of them involved in the control of cell division and proliferation. The AKT pathway also results in the activation of IκB kinase beta (IKKβ), which gives rise to NF-κB activation. IFNs-I also activate NF-κB by an alternative pathway, which involves the linkage of TNF receptor–associated factors (TRAF) to the activation of the NF-κB–inducing kinase (NIK), which in turn results in activation of NF-κB2. This alternative pathway is strictly dependent on the activity of IKKα. In addition, PI3K/AKT can also activate NF-κB through an activation loop via protein kinase C zeta (PKCζ). Overall, NF-κB activated by IFNs-I regulates prosurvival signals and enhances the expression of several GTP-binding proteins as well as molecules involved in antigen processing and/or presentation.

**The MAPK pathway.** Activation of JAK results in tyrosine phosphorylation of the guanine nucleotide exchange factor Vav, which leads to downstream activation of Rat sarcoma protein (Ras) and ras-related C3 botulinum toxin substrate 1 (Rac1), which subsequently leads to the activation of several MAPKs: p38, c-Jun N-terminal kinases (JNK), and extracellular signal regulated kinases (ERK) 1 and 2 (9). Vav can also activate PKCζ, leading to the activation of the NF-κB cascade. Several studies have shown that IFN-α–mediated activation of ERK1/2 in T lymphocytes requires proteins involved in the T-cell receptor (TCR) early signaling complex, such as CD45, lymphocyte-specific protein tyrosine kinase (Lck), Zeta-chain-associated protein kinase 70 (Zap70), SH2 domain-containing leukocyte protein of 76 kDa (SLP76), and Vav1, and possibly linker for activation of T cells (LAT), indicating cross-talk between pathways (29–31). Moreover, it has been shown recently that TCR deletion in Jurkat cells abrogated IFNAR–stimulated MAPK activity, whereas the canonical JAK-STAT pathway remained unaffected (31). A hypothetical pathway that involves all these molecules and results in Vav activation is depicted in Fig. 1D. The different MAPKs activate different sets of transcription factors. Importantly, p38 functions are essential for the antiviral and antileukemic properties of IFNs-I, it plays a role in the hematopoietic-suppressive signals and is required for the growth-inhibitory effects of IFNs-I observed in certain lymphocyte cultures. IFNs-I–activated ERK cascades regulate cellular growth, differentiation, and serine phosphorylation of STAT1. The search for biochemical signals to explain the effects of IFN-I on immune system cells is far from over.

**Effects of IFNs-I on cells of the immune system**

It has long been established that the main mechanism accounting for the efficacy of the IFN-I–based therapies was due to their direct effect on malignant or virus-infected cells. In fact, IFNs-I directly inhibit the proliferation of tumor and virus-infected cells and increase MHC class I expression, enhancing antigen recognition. Moreover, IFNs-I repress oncogene expression and induce that of tumor suppressor genes, which may contribute to the
inhibitory effects of IFN-I on malignant cells in conjunction with the antiangiogenic effects.

IFNs-I have also proven to be involved in immune system regulation (7, 8, 32). IFNs-I exert their effects on immune cells either directly, through IFNAR triggering, or indirectly (i) by the induction of chemokines, which allow the recruitment of immune cells to the site of infection; (ii) by the secretion of a second wave of cytokines, which could further regulate cell numbers and activities (as for example IL-15, which plays a critical role in proliferation and maintenance of NK cells and memory CD8 T cells; refs. 33, 34); or (iii) by the stimulation of other cell types critical for the activation of certain immune cells, such as DC for the activation of naïve T cells.

One of the earliest described immunoregulatory functions of IFNs-I was their ability to regulate NK functions (32). IFNs-I enhance the ability of NK cells to kill target cells and to produce IFN-γ by indirect and direct mechanisms (33, 35, 36). Furthermore, IFNs-I promote the accumulation and/or survival of proliferating NK cells by the IFN-I/STAT1-dependent induction of IL-15 (33). IFNs-I also enhance the production or secretion of other cytokines by the NK cell through the autocrine IFN-γ loop (37).

IFNs-I also affect monocyte and/or macrophage function and differentiation. Thus, IFNs-I markedly support the differentiation of monocytes into DC with high capacity for Ag presentation, stimulate macrophage antibody-dependent cytotoxicity, and positively or negatively regulate the production of various cytokines (e.g., TNF, IL-1, IL-6, IL-8, IL-12, and IL-18) by macrophages (38). In addition, autocrine IFN-I is required for the enhancement of macrophage phagocytosis by macrophage colony-stimulating factor and IL-4 (39) and for the lipopolysaccharide, virus-, and IFN-γ-induced oxidative burst through the generation of nitric oxide synthase 2.

The main function of DCs is to uptake and process antigens for presentation to T cells. DCs are a unique cell type able to prime naïve T cells and, therefore, are critical antigen presenting cells (APC). IFNs-I have multiple effects on DCs, affecting their differentiation, maturation, and migration. Thus, human monocytes cultured in granulocyte-macrophage colony-stimulating factor (GM-CSF) + IFN-α/β, rather than the more commonly used combination of GM-CSF + IL-4, differentiate more rapidly into DCs, exhibiting the phenotype of partially mature DCs, while showing a strong capability to induce a primary human antibody response and CTL expansion when pulsed with antigen and injected into humanized severe combined immunodeficiency (SCID) mice (40–42).

In vitro treatment of immature conventional DCs with IFN-α/β has been shown to upregulate surface expression of MHC class I, class II, CD40, CD80, CD86, and CD83 molecules in the human system (43–45), associated with a heightened capacity to induce CD8 T-cell responses. Accordingly, it has been observed in mice that IFN-α acting on DC plays a key role in achieving efficient cross-priming of antigen-specific CD8 T lymphocytes (7, 8, 32). IFNs-I also affect the ability of DC to secrete IL-12p70. Low concentrations of IFNs-I are essential for the optimal production of IL-12p70 (46), whereas higher levels of IFN-I suppress IL-12p40 expression, thus dampening IL-12p70 production (47).

A key requisite to initiate the adaptive immune response is the arrival of professional APC from infected tissue into lymph nodes. It has been shown that human DCs differentiated from monocytes in the presence of IFN-α exhibit upregulation of CC chemokine receptor type 7 (CCL7), correlating with an enhanced chemotactic response in vitro to CCL7 natural ligand (CCL19) and with strong migratory behavior in SCID mice (48). Interestingly, experiments in mice have also shown that IFN-α/β is required for plasmacytoid DCs (pDC) to migrate from the marginal zone into the T-cell area, where they form clusters (49). We have also recently shown that IFNs-I enhance the adhesion and extravasations of DCs across inflamed lymphatic endothelium in a lymphocyte function-associated antigen 1 (LFA-1)− and very late antigen-4 (VLA4)−dependent fashion (50). IFNs-I may also favor the encounter between DCs and specific lymphocytes in lymph nodes by promoting lymphocyte trapping in lymph nodes upon downregulation of sphingosine 1-phosphate (51).

IFNs-I have also been shown to potently enhance the primary antibody response to soluble antigen, stimulating the production of all subtypes of immunoglobulin G (IgG), and inducing long-lived antibody production and immunologic memory (8). Direct effects of IFN-α on DCs (8), B cells (52, 53), and CD4 T cells (53) all contribute to its adjuvant activities on humoral immune responses. Interestingly, a direct effect of IFNs-I on B cells seems to be crucial for the development of local humoral responses against viruses (54).

As mentioned above, CD4 T cells are direct targets of IFN-I in the enhancement of antibody responses (53). In humans, it has also been described that direct effects of IFN-I on naïve CD4 T cells favor their differentiation into IFN-γ-secreting Th1-like T cells (55).

Several studies suggested that IFNs-I might exert a direct effect on CD8 T cells. Thus, it was reported that IFNs-I promote IFN-γ production by CD8 T cells in a STAT4-dependent manner (56) and promote survival of CD8 T cells from wild-type (WT) but not IFNAR-deficient (IFNAR−/−) mice (57). The definitive report showing that CD8 T cells represent direct targets of IFN-I−mediated stimulation in vivo came from Kolumam and colleagues (58). By adoptively transferring virus-specific CD8 T cells from IFNAR−/− or IFNAR-sufficient mice into normal IFNAR WT hosts, IFNs-I were shown to act directly on murine CD8 T cells, allowing their clonal expansion and memory differentiation. Subsequent studies confirmed this work (59–61). Elegant experiments in mice by Curtssinger and colleagues (62) have shown that, in addition to signals via TCR (signal-1) and CD28 (signal-2), naïve CD8 T cells required a third signal to differentiate into effector cells. cDNA microarray analyses showed that IFN-α could regulate critical genes involved in CTL functions (63), providing evidence that IFNα promoted activation and
difficulties of CD8 T cells by sustaining the expression of T-bet and Eomes through chromatin remodeling. Recently, we have shown that IFN-α provides a strong and direct signal to human CD8 T cells, thereby resulting in upregulation of critical genes for cytotoxic T-cell activity (cytolysis and IFN-γ secretion) and for the production of chemokines that would attract other effector lymphocytes. IFN-α was absolutely critical in the case of human naïve CD8 T cells for effector function acquisition (64). In many instances, T cells may sense IFN-I before the cognate antigen is actually presented to them. As a result of a preexposure to IFN-I, CD8 T cells become preactivated and acquire much faster effector functions upon antigen recognition (65). This preactivation may reflect the upregulation by IFN-I of several mRNAs in antigen-naïve CD8 T lymphocyte, albeit without changes in the expression of the corresponding protein, unless antigen-specific activation ensues (64).

Clinical-Translational Advances

The contracting current indications of IFN-α as an anticancer agent

IFN-α has received approval for treatment of several neoplastic diseases (66). The most frequent indications for IFN-α are chronic viral hepatitis. For the treatment of these infectious conditions, stabilized forms of IFN-α have been created by directed conjugation of polyethylene glycol, which, by increasing molecular weight, retards renal clearance and, thereby, extends plasma concentrations with sustained receptor occupancy (67). However, PEG-conjugated IFN is not widely used in oncology in the absence of sustained receptor occupancy (67). However, PEG-conjugated IFN is not widely used in oncology in the absence of sustained receptor occupancy (67).

In oncology, the main indication of IFN-α is for patients with resected stage II and III melanoma, in whom IFN-α prolongs disease-free survival and shows a trend toward increased overall survival (68). However, the advent of CTLA-4 antagonist antibodies will very likely displace the use of IFN-α for melanoma therapy (69).

Table 1 shows the spectrum of neoplastic diseases in which IFN-α has been used. As shown, its role in cancer therapy is steadily decreasing because of its limited efficacy and the advent of new, more effective, and/or safer treatments.

Future perspectives

IFNs-I are powerful tools to directly and indirectly modulate the functions of the immune system. Evolution has shaped these cytokines as a key sign of alarm in case of viral infection. The type of immune response that we would like to induce and sustain against cancer antigens is identical to the one we commonly observe upon acute viral infections. Obviously, the effects of IFN-I are integrated with many other key molecules that need to act in a concerted fashion.

As described in Table 1, side effects of systemic long-term treatments and lack of sufficiently high efficacy have dampened the interest of IFN-α for clinical use in oncology. However, we believe that IFN-α is likely to be more efficacious when acting locally and intermittently at the malignant tissue and tumor-draining lymph node than when administered to achieve systemic bioavailability. Local delivery can be achieved with pharmaceutical formulations and gene therapy approaches (70). In our opinion, the clinical use of recombinant IFN-α as a vaccine adjuvant should be reconsidered and new investigations carried out with an eye to clinical applications (71).

The rationale for using intermittent delivery arises from observations indicating that IFN-I turns on signaling desensitizing mechanisms (i.e., because of SOCS1 induction). Immittency at an optimized pace may help to avoid these negative feedback mechanisms in the responding immune cells. These ideas contrast with stabilized formulations, such as the widely used polyethylene glycol-conjugated IFN-α and fusion proteins with albumin that extend the half-life of the cytokine.

It is of much interest that a gene expression signature induced by IFN-I in melanoma lesions predicts benefit from vaccines and may have a key role in recruiting effector T cells to tumors by inducing chemokine genes (72). IFN-α has been recently used in promising combinatorial immunotherapy approaches alongside DC vaccination for glioblastoma, precisely to promote T-cell infiltration and DC activation (73). In this regard, using endogenous IFN-I inducers instead of recombinant cytokines may have advantages, because substances such as the viral RNA analog poly I:C will also elicit other cytokines that may act in concert with IFNs-I to enhance the antitumor immune response.

Creative combination strategies are building on the knowledge that IFN-α effects on the immune system are likely to improve its therapeutic profile against malignant diseases. For instance, combinations with immunostimulatory monoclonal antibodies, IL-15, IL-12, and IL-21, may hold much promise. Indeed, intratumoral release of mouse IFN-α along with systemic treatment with anti-CD137 mAb results in synergistic therapeutic effects (74). Macrophages homing to tumor, transduced to express IFN-α, exert therapeutic effects without the systemic side effects (75). These studies suggest that local delivery as opposed to systemic administration should be tested. Of great importance is the notion that the chemokines induced by IFN-I (i.e., CXCL9, CXCL10) attract activated lymphocytes, thereby calling more immune cells to infiltrate the malignant focus.

When reflecting on the use of IFN-I for cancer, we must think about reprogramming the tumor microenvironment, frequently devoid of any stimulatory signals. Local IFN-I release with concomitant irradiation and chemotheraphy may help to turn some of the macroscopic tumor lesions into immunogenic vaccines. Factors such as CpG oligonucleotides or poly I:C that induce the release of endogenous IFNs-I at a given tumor lesion (76) are promising in this regard. These agents may constitute an advantageous alternative because these agents also induce an additional array of proinflammatory mediators acting in synergy with IFNs-I.
<table>
<thead>
<tr>
<th>Indication</th>
<th>Stage</th>
<th>Comment</th>
<th>Standard Current Therapy</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>II/III</td>
<td>Prolongs disease-free survival and shows a trend toward increased overall survival.</td>
<td>IFN-α is the standard option.</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>Combination with IL2: Increased response rates but no survival improvement.</td>
<td>Chemotherapy. The advent of CTLA-4 antagonist antibody will displace the use of IFN-α for melanoma immunotherapy.</td>
<td>77, 78</td>
</tr>
<tr>
<td>RCC</td>
<td>II/III</td>
<td>Two phase III trials showed negative results.</td>
<td>Novel targeted agents such as sunitinib, temsirolimus, sorafenib, or everolimus have decreased the use of IFN-α to a minimum in both resectable and advanced RCC.</td>
<td>79, 80</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>Widely studied as a single agent or in combination with IL-2, chemotherapy, or both: modest or negative results.</td>
<td></td>
<td>81</td>
</tr>
<tr>
<td>Hairy cell leukemia</td>
<td></td>
<td>First treatment that showed clinical benefit in this disease.</td>
<td>Purine analogs are now considered standard treatment for this disease.</td>
<td>82, 83</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recommended, in low dose, as a therapeutic option for maintenance therapy and as an alternative for frail patients.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td></td>
<td>Extensively studied as maintenance treatment, as single treatment, or in combination with chemotherapy: slight efficacy.</td>
<td>Largely replaced by newer and more effective agents such as thalidomide, lenalidomide, or bortezomib.</td>
<td>84</td>
</tr>
<tr>
<td>CMS</td>
<td>PV</td>
<td>Optional treatment for cytoreduction (94.6% complete responses).</td>
<td>The mainstay of therapy remains repeated phlebotomy.</td>
<td>85–87</td>
</tr>
<tr>
<td></td>
<td>ET</td>
<td>Treatment of choice in women with childbearing potential and optional treatment in young patients resistant to hydroxyurea.</td>
<td>Hydroxyurea. Anagrelide.</td>
<td>86</td>
</tr>
<tr>
<td>CML</td>
<td>PM</td>
<td>Cytoreduction therapy. First-line therapy in combination with cytarabine: 71% clinical response rate and 39% major cytogenetic response rate.</td>
<td>Hydroxyurea. Thalidomide. Imatinib, in a phase III trial, has been superior in tolerability, complete hematologic and cytogenetic response rates, and progression-free survival.</td>
<td>77, 88–92</td>
</tr>
</tbody>
</table>
In conclusion, the notion of key direct effects of IFNs-I on immune system cells and detailed knowledge on the elicited signaling pathways should help biomarker discovery to identify the small number of patients who could actually benefit from current treatments. More importantly, these ideas might change the way we use IFN-α for cancer therapy, suggesting new strategies and combinations with other agents.

Disclosure of Potential Conflicts of Interest

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Table 1. Contracting Indications of IFN-α for Malignant Conditions (cont’d)

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<thead>
<tr>
<th>Indication</th>
<th>Stage</th>
<th>Comment</th>
<th>Standard Current Therapy</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemangioma</td>
<td></td>
<td>Complicate hemangiomas that do not respond to steroids. Rate regression in 58% of the patients.</td>
<td>Steroids.</td>
<td>93</td>
</tr>
<tr>
<td>AIDS-related Kaposi sarcoma</td>
<td></td>
<td>Evidence for clinical activity. Liposomal anthracyclines are preferred as the first treatment option.</td>
<td></td>
<td>94</td>
</tr>
</tbody>
</table>

PV, polycythemia vera; ET, essential thrombocythemia; PM, primary myelofibrosis; RCC, renal cell cancer; CMS, chronic myeloproliferative syndrome; CML, chronic myeloid leukemia

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