International Research Journal of Basic and Clinical Studies Vol. 7(3) pp. 1-3, June, 2022
Available online http://www.interesjournals.org/IRJBCS

Review Article

Clinical Toxicity of Interferon in Cancer Patients

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Received: 03-Jun-2022, Manuscript No. IRJBCS-22-69096; **Editor assigned:** 06-Jun-2022, Pre-QC No. IRJBCS-22-69096 (PQ); **Reviewed:** 20-Jun-2022, QC No.IRJBCS-22-69096; **Revised:** 25-Jun-2022, Manuscript No. IRJBCS-22-69096 (R); **Published:** 30-Jun-2022 , DOI: 10.14303/irjbcs.2022.12

Abstract

Interferon (IFN) has been designated as a typical biological response modifier (BRM). Like corticosteroids, they cause a variety of physiological changes [1]. Therefore, IFNs act through a mechanism different from conventional cell proliferation inhibitors, and their therapeutically optimal doses in cancer treatment may not necessarily correspond to the maximum tolerated dose. Optimal treatment for cancer includes different treatments and combinations of different medicines. Experimental studies have shown that IFN can be effectively combined with radiation and chemotherapy. In addition, IFN enhances mutual effects and the effects of other biopharmaceuticals. [2] Such a new combination approach provides an opportunity to overcome the resistance of malignant cells. Preliminary evidence from Phase I and II studies shows that qualitatively similar clinical toxicity occurs in IFNα, IFNβ and IFNγ. Untreated to further define the clinical spectrum of adverse events associated with different types, doses, and schedules of IFN immunotherapy and combination therapy, and to select a series of routine tests to monitor IFN toxicity. Four phase II trials from a study of 43 lung cancer patients [3].

IFN-I in combination therapy

There is increasing literature showing that the antitumor response induced by chemotherapy and radiation therapy, at least in part, depends on the activation of IFN-I in cancer and immune cells (as outlined in). In particular, animal model data suggest that IFN-I can regulate the immunogenicity of cell death induced by specific cytotoxic anticancer treatments [4]. For example, cisplatin, a drug that cannot induce immunogenic cell death (ICD), cannot induce defensive antitumor immunity in cancer-bearing mice unless preceded by intratumoral injection of IFN-I. IFN-I may also provide added value in combination with IFN-I and chemotherapeutic agents known to induce ICD. Cross-presentation of tumor antigens to cells (DC) and subsequent CD8 + T cells. These data, and other data reviewed in , show that IFN-I acts synergistically not only with chemotherapy, but also with radiation therapy by multiple mechanisms that affect apoptosis [5], ICD, and immune cells. It leads to the concept of being able to do it. The results of preliminary studies on the combination of IFN and chemotherapy / radiation therapy were promising, but because they were hampered by toxicity, timing and timing should be considered when considering how IFN-I should be used in a new generation of combination therapy. Special attention should be paid to the administration of the exposure dose. Discontinuous administration of IFN-I ensures transient and acute exposure of TME to cytokines, avoiding not only toxicity but also phenomena such as IFN downregulation-I receptors and potential immunosuppression, while ICD and most likely to promote DC activation [6]. induced under chronic activation of the IFN-I system.

IFN-I and Epigenetics

In cancer cells, IFN-I increases cytokine DNA-induced accumulation, cyclic GMP-AMP synthase (cGAS) / IFN gene stimulator (STING) pathway activation, and immunogenic cancer antigen, HLA class I. , Restricted antigen presentation and restricted downstream production of IFN-I and pro-inflammatory cytokines [7]. Interestingly, "virus mimicry" has been shown to be induced by epigenetic inhibitors (EPIi) such as DNA methyltransferase inhibitors (DNMTi) and histone deacetylase inhibitors (HDACi) [29]. .. By activating IFN-I signaling, EPIi strongly regulates the tumor microenvironment and reduces immunosuppressive signaling [30]. This evidence underscores the important role of epigenetic regulation in the constitutive and inducible expression of IFN-I and IFN-stimulating genes [8]. Given its potent antitumor effects in some hematological

malignancies, the FDA has approved various DNMTi and HDACi clinical uses. However, DNMTi and HDACi as monotherapy were ineffective in most solid tumors. Nevertheless, due to their strong immunomodulatory effects, promising results are expected from the combination with ICI [9]. From this perspective, the more rational use of EPIi alone or in combination may represent a new therapeutic frontier for enhancing the therapeutic activity of IFN-I. The combination of EPIi and IFN-I is supported by some preclinical data. The potential complementary antitumor activity of EPIi and endogenous or extrinsic IFN-I takes into account important unanswered variables such as the correct ordering of treatments and the harmful immunosuppressive effects that may occur. Further investigation is needed.

IFN-α in DC-based combination immunotherapy

Much of the data published over the last two decades indicate that IFN-I is an important factor in inducing rapid differentiation and activation of DC in both mouse and human models (reviewed in), and IFN- It shows that DC interactions can play an important role. In antitumor immune response. In particular, monocytes cultured for a short time in GM-CSF and IFN-α produce DC called IFN-DC, take up apoptotic tumor bodies, and induce strong tumor-specific T cell immunity Indicates [10]. We utilized the use of these cells in two pilot clinical trials (melanoma and follicular lymphoma) in combination with insitu vaccination and lethal agents aimed at overcoming immunosuppressive signals. Interestingly, activation of antitumor response and objective clinical response were observed in most patients, demonstrating that this approach is a valuable tool for enhancing antitumor response. In particular, recent studies have shown that effective antitumor responses to anti-PD1 antibodies include the presence of IL-12-producing intratumoral DCs and the clear interaction between NK cells and DCs in the tumor microenvironment. It has been shown that is strictly required. Interestingly, IFN-DCs are potent IL-12-producing cells [56], and given recent evidence of the role of intratumoral IL-12-producing DCs in mediating the response to ICI , anti-PD1 Can be a good candidate for augmenting. Base treatment [11]. We envision a treatment scenario in which a cancer patient is treated with IFN-DC as unloaded antigen-presenting cells injected into the tumor or as in vitro antigen-loaded DC injected with anti-PD1 thereafter**.**

IFN-I in antitumor therapy targeting cancer stem cells (CSCs)

Recent studies have highlighted the unexpected relationship between IFN-I and CSC, opening up prospects for the design of new antitumor therapies. IFN-I's involvement in CSC retention has recently been reported in our group and other breast cancer models [12]. In Her2 / Neu transgenic mice, impaired IFN-I signaling increased mammary CSC levels during spontaneous carcinogenesis. In addition to being consistent with experimental data showing the close relationship between IFN-I and CSC , these results show that impaired IFN-I signaling reduces the clinical outcome of cancer and reduces therapeutic response. It supports clinical data showing that it is associated with . Evidence has accumulated for the specific role of IFN-β in breast cancer CSC stem cellity, even when administered at low doses, through transcriptional regulation of CSC differentiation as well as immunomodulatory mechanisms. A further step in the IFN-I study requires a final analysis of the role of endogenous and extrinsic IFN-I in the biology of CSCs in a variety of clinical environments. For breast cancer, IFN-β appears to be the best candidate to be tested with clinical protocols aimed at preventing tumor recurrence in an adjuvant setting. It envisions continuous (or semi-continuous) treatment with low-dose cytokines, which guarantees recovery of basal levels of cytokines that may be suppressed by the tumor.

IFN-I as an immune adjuvant for cancer vaccines

The main research agenda for cancer vaccine development involves identifying optimal strategies for reversing immunosuppression in cancer patients and enhancing the immune response to tumor antigens. Studies of mouse and human models conducted by our group and others over the last 20 years have shown that IFN-I is due to multiple mechanisms, including in vivo differentiation / activation of DC and references therein. (Suggests to be mediated) Vaccine adjuvant. In particular, IFN-I has been used in pilot studies as a vaccine adjuvant for human infectious diseases and neoplastic diseases (references reviewed in. In patients with advanced melanoma, vaccination of melanoma peptides in combination with locally and simultaneously administered low-dose IFN-α enhances activation of specific CD8 + T cells and monocyte / DC progenitor cells. It brought about [13] and was shown to bring about promising clinical practice. Benefits in the absence of significant toxicity (Urbani et al., Submitted). In these two studies of patients with advanced melanoma, IFN-α2b (3-6 million units) s.c. Administration. Injection of melanoma peptides with the primary purpose of inducing DC activation during repeated i.d. and thereby promoting an antitumor immune response. We believe that the development of more potent cancer vaccines should consider the potential contributions of IFN-I and IFN-I inducers used as local immune adjuvants.

IFN-α in DC-Based Combination Immunotherapy

An ensemble of data published over the last two decades have shown that IFN-I are important factors for inducing a rapid differentiation and activation of DC in both mouse and human models (reviewed in) and that IFN-DC interactions can play key roles in the antitumor immune response [14]. Of note, monocytes short-term cultured with GM-CSF and IFN-α generate DC, named IFN-DC, with a unique attitude to take-up tumor apoptotic bodies and induce a potent tumor specific T cell immunity . We exploited the use of these cells in two pilot clinical trials (in melanoma and follicular lymphoma) in combination with death-inducing

agents aiming at in situ vaccination and the overcoming of immunosuppressive signals . Interestingly, we observed activation of the anti-tumor response and objective clinical response in a large portion of patients, thus pointing to this approach as a valuable tool to increase antitumor response. Notably, recent studies have shown that an effective antitumor response to anti-PD1 antibodies strictly requires the occurrence of intratumoral DC producing IL-12 [15], and well-defined interactions between NK cells and DC in the tumor microenvironment [16].

ACKNOWLEDGEMENT

This article published the first report of the antitumor effect of IFN-I in mice 50 years ago, and Ion Gresser, a mentor and friend of one of us (FB) who died on April 9, 2019 Dedicated to.

CONCLUSIONS

After more than 50 years since the initial demonstration of the antitumor effects of IFN-I in mice, we are still discovering new and important functions of these cytokines in cancer, suggesting novel rationales and modalities for their clinical use. In particular, the use of older drugs, either in new therapeutic applications or in qualitatively new modalities, is approved for new drugs in terms of cost and impact on the public health system, thanks to the reduced cost and time required for clinical development. It is more advantageous than.

Today, given advances in understanding the mechanism of action, the combination of various immunotherapies with traditional and new drugs and therapies is crucial for the development of more effective and personalized cancer therapies. Is unanimously considered [59]. As shown in Figure 4, the expression level of endogenous IFN-I is consistent with a complex balance of TME immune infiltration and immunosuppression, with different scenarios showing different responses to currently available cancer therapies.

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