Interferon α may be back on track to treat acute myeloid leukemia

Evelien L.J.M. Smits, Sébastien Anguille and Zwi N. Berneman

Tumor Immunology Group; Laboratory of Experimental Hematology; Vaccine and Infectious Disease Institute; Faculty of Medicine and Health Sciences; University of Antwerp; Antwerp, Belgium; Center for Cell Therapy and Regenerative Medicine; Antwerp University Hospital; Antwerp, Belgium

Abstract

Starting in 1966 (with a peak in the 1980s and 1990s), the results of no less than 34 clinical studies on the antineoplastic activity of interferon α (IFNα) in acute myeloid leukemia (AML) patients have been published.1-3 IFNα has been tested in three different therapeutic settings: (1) for the induction of AML remission, (2) as a salvage therapy for the treatment of patients relapsing upon hematopoietic stem cell transplantation (HSCT), and (3) as a post-remission strategy to prevent recurrence.1 Although objective clinical responses were observed in all such settings, reported clinical outcomes are considerably heterogeneous, probably linked to similarly heterogeneous study designs. As a consequence, firm conclusions about the therapeutic role of IFNα could not be made, explaining why IFNα did not become a standard treatment option for AML patients.1

Nevertheless, there is a biological rationale for the use of Type I IFN (IFNα or IFNβ) to treat AML (Fig. 1).1 First, Type I IFN exerts direct antitumor effects on AML cells by multiple mechanisms, as it (1) limits the secretion of growth-promoting cytokines, (2) stimulates apoptosis, (3) inhibits cell proliferation, and (4) increases the immunogenicity of AML cells. Second, Type I IFN exerts indirect antitumor effects by activating dendritic cells (DCs), natural killer (NK) cells and T cells, three cell types that play a major role in antitumor immune responses. In this context, a recent report has shown that Type I IFN is critical to the initiation of antitumor immunity through direct actions on cross-presenting DCs.4 In addition, IFNα, similar to interleukin-15,5 can induce DCs to become killer cells and hence exert direct cytotoxic activity against AML cells.6,7

Why has IFNα failed to show consistent clinical benefit in AML patients, in spite of the conceptual background supporting its potential efficacy? A preclinical study performed by Benjamin et al.8 identified what could have made the difference between treatment success or failure. According to this study, high IFNα serum levels (at least 3000 IU/mL) during a prolonged period seem to be a prerequisite for treatment success in AML.1,8 Thus, the therapeutic potential of IFNα can perhaps be unlocked by the use of long-acting IFN preparations, such as IFNα conjugated to a polyethylene glycol moiety (pegylated-IFNα). Such modified IFNα preparations have an improved pharmacokinetic profile that allows for the protracted maintenance of high and stable serum IFNα levels.

We tested pegylated IFNα-2a in a patient affected by AML secondary to myelofibrosis who turned down chemotherapy and HSCT.2 After 5 mo of treatment with at least 180 μg pegylated IFNα-2a per week, bone marrow analyses showed complete AML remission. This remission lasted for more than 3 y and the patient is still alive after 4 y, far longer than the expected 6-mo survival after diagnosis.9 Currently, high doses of pegylated IFNα-2a are required to keep leukemia under control in this patient.

Following our study, Dagorne et al.5 reported the induction of complete hematological remission in a patient affected by AML secondary to essential thrombocytemia who received pegylated IFNα-2a at a dose of 180 μg per week. This regimen was continued for 13 mo until HSCT. The overall survival of this patient was 18 mo and death was due to HSCT-related complications.

IFNα-based immunotherapy has been shown to exert remarkable effects in patients affected by BCR/ABL-negative...
especially in cases in which AML is secondary to myeloproliferative neoplasms and in elderly patients that are not eligible for aggressive chemotherapy.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

IFNα in its pegylated form exerts a therapeutic activity against AML in general and remains to be determined in clinical trials. However, the data reported above coupled to the generally low toxicity of pegylated IFNα-2a provide a rationale for the use of this immunotherapeutic agent in AML patients with poor prognosis, especially in cases in which AML is secondary to myeloproliferative neoplasms and in elderly patients that are not eligible for aggressive chemotherapy.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

References
1. Anguille S, Lion E, Willemen Y, Van Tendeloo VE, Berneman ZN, Smits EL. Interferon-α in acute myeloid leukemia: an old drug revisited. Leukemia 2011; 25:739-48; PMID:21274002; http://dx.doi.org/10.1038/leu.2010.324
2. Berneman ZN, Anguille S, Van Marck V, Schroyens WA, Van Tendeloo VE. Induction of complete remission of acute myeloid leukemia by pegylated interferon-alpha-2a in a patient with transformed primary myelofibrosis. Br J Haematol 2010; 149:152-5; PMID:19993392; http://dx.doi.org/10.1111/j.1365-2141.2009.08025.x
3. Dagorne A, Douet-Guilbert N, Quintin-Roue I, Guillemin G, Couturier MA, Berthou C, et al. Pegylated interferon α2a induces complete remission of acute myeloid leukemia in a postessential thrombocytopenia myelofibrosis permitting allogeneic stem cell transplantation. Ann Hematol 2013; 92:407-9; PMID:22941306; http://dx.doi.org/10.1007/s00277-012-1560-9
4. Diamond MS, Kinder M, Matsushita H, Mashayekhi M, Dunn GP, Archambault JM, et al. Type I interferon is selectively required by dendritic cells for immune rejection of tumors. J Exp Med 2011; 208:1989-2003; PMID:21930709; http://dx.doi.org/10.1084/jem.20101158
5. Anguille S, Lion E, Tel J, de Vries IJ, Couderé K, Fromm PD, et al. Interleukin-15-Induced CD56(+) Myeloid Dendritic Cells Combine Potent Tumor Antigen Presentation with Direct Tumoricidal Potential. PLoS One 2012; 7:e51851; PMID:23284789; http://dx.doi.org/10.1371/journal.pone.0051851
6. Papewalis C, Jacobs B, Wünke M, Ullrich E, Baehring T, Fenk R, et al. IFN-alpha skews monocytes into CD56+-expressing dendritic cells with potent functional activities in vitro and in vivo. J Immunol 2008; 180:1462-70; PMID:18209041
7. Roethans D, Smits E, Lisio E, Tel J, Anguille S. CD56 marks human dendritic cell subsets with cytotoxic potential. OncolImmunology 2013; In press; http://dx.doi.org/10.4161/onci.23037

8. Benjamin R, Khwaja A, Singh N, McIntosh J, Meager A, Wadhwa M, et al. Continuous delivery of human type I interferons (alpha/beta) has significant activity against acute myeloid leukemia cells in vitro and in a xenograft model. Blood 2007; 109:1244-7; PMID:17047156; http://dx.doi.org/10.1182/blood-2006-02-002915

9. Mesa RA, Li CY, Ketterling RP, Schroeder GS, Knudson RA, Tefferi A. Leukemic transformation in myelofibrosis with myeloid metaplasia: a single-institution experience with 91 cases. Blood 2005; 105:973-7; PMID:15388582; http://dx.doi.org/10.1182/blood-2004-07-2864

10. Kiladjian JJ, Chomienne C, Fenaux P. Interferon-alpha therapy in bcr-abl-negative myeloproliferative neoplasms. Leukemia 2008; 22:1990-8; PMID:18843285; http://dx.doi.org/10.1038/leu.2008.280