INTERFERing with the progression of T-cell acute lymphoblastic leukemia: a multifaceted therapy

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In this issue of *Haematologica*, a new manuscript by Goosens *et al.*[1] elegantly dissects the direct and indirect therapeutic effects of type-I interferons (IFN-I) in the treatment of T-cell acute lymphoblastic leukemia (T-ALL). Even if advances in T-ALL treatment in the last decades have resulted in high cure rates, 20-50% of patients still relapse and ultimately die, underscoring the need to identify novel therapeutic strategies and to properly stratify patients who might respond to specific targeted agents.[2] Interferons have been widely used in the treatment of both solid and hematologic tumors because of their multiple anticancer properties, which include direct cancer cell-intrinsic cytostatic/cytotoxic effects, as well as immune system-mediated cancer cell-extrinsic effects.[3] However, IFN-I therapy in cancer has typically resulted in uneven and unreliable results given the poor anticancer properties of these compounds in some tumors together with complex side effects due to their pleiotropic activity.[4]

In order to assess the direct anticancer activity of IFN-I in T-ALL, Goossens and colleagues treated different human T-ALL cell lines as well as T-ALL patient-derived xenografts with human IFN-I, both *in vitro* and *in vivo*. Consistent with previous literature,[5] the antileukemic effects of IFN-I stimulation were only observed in samples that showed JAK/STAT1 activation upon treatment with IFN-I, as measured by pSTAT1 intracellular staining. These results suggest that this fast and easy method to analyze pSTAT1 levels in patients' cells *in vitro* could be used as a biomarker to stratify patients who might respond to IFN-I treatment.

In order to assess the indirect anticancer effects of IFN-I in T-ALL, authors then used a model of PTEN-null and IFN-I-sensitive mouse primary leukemia, upon transplantation into immunocompetent or immunodeficient recipients. These experiments showed that, even if murine IFN-I treatment resulted in antileukemic effects with extended survival in both settings, its therapeutic effects were much stronger in the presence of an intact immune system, demonstrating its significant immune-mediated cell-extrinsic antileukemic effects. Next, authors used activity-on-target interferons (AcTaferons; AFN)[6] in order to specifically direct the activity of IFN-I to $CD8^+$ murine cells (mCD8-AFN), given that roughly half of T-ALL are $CD8^+$ and, moreover, CD8 is also expressed by mouse classical dendritic cells type I (cDC1), which are relevant for triggering a CD8 cytotoxic response (CTL) upon IFN-I stimulation.[7] In this context, as expected, mCD8-AFN treatment in immunodeficient mice resulted in antileukemic effects only when these mice harbored $CD8^+$, not $CD8^-$, mouse leukemias. However, rather unexpectedly, similar results were also obtained when these $CD8^+$ or $CD8^-$cells were transplanted into immunocompetent mice. By contrast, when authors used a different AFN directed at Clec9a (mClec9a-AFN), which has been shown to elicit a cDC1-mediated antitumor response in other tumors,[7] significant antileukemic effects were observed *in vivo* in immunocompetent mice harboring both $CD8^+$ or $CD8^-$ leukemias. Importantly, mClec9a treatment even resulted in 20-40% cure rates, while no leukemic mice were cured either by mCD8-AFN or mIFN treatment itself. Interestingly, and as expected (given that Clec9a is not expressed in normal or malignant T cells), this antileukemic effect was completely absent if these leukemias were transplanted into immunodeficient mice, highlighting that mClec9a-AFN antileukemic effects are driven exclusively by immune system-mediated antitumor responses.

These results showing strong indirect effects for mClec9a-AFN but reduced/absent effects for mCD8-AFN are intriguing. Previous studies showed that IFN signaling in dendritic cells, but not in T cells, is required for AFN antitumor activity, however, optimal antitumor effects of AFN are still dependent on the presence of $CD8^+$ cytotoxic T cells (CTL),[8] and priming and activation of CTL requires prior activation and maturation of dendritic cells. One possible explanation of these discordant results might be that binding of the mCD8-AFN on CTL could neutralize their cytotoxic properties; however, this is unlikely since mCD8-AFN was previously shown to have significant additive antitumor effect in combination with tumor necrosis factor-based targeted therapy.[9] Moreover, in the study by Goosens *et al.*[1] mCD8-AFN treatment seemed to translate into improved antileukemic effects in $CD8^+$ leukemias transplanted into immunocompetent mice, as compared to immunocompromised mice. Another interesting but bizarre possibility to reconcile these results might be that, in order to elicit its indirect immune-mediated effects, mCD8-AFN treatment might first require some direct cell-intrinsic effects to take place, which would thus explain indirect effects being observed only on $CD8^+$ leukemias. Finally, it is also possible that mCD8-AFN does not activate cDC1 cells to the same extent as

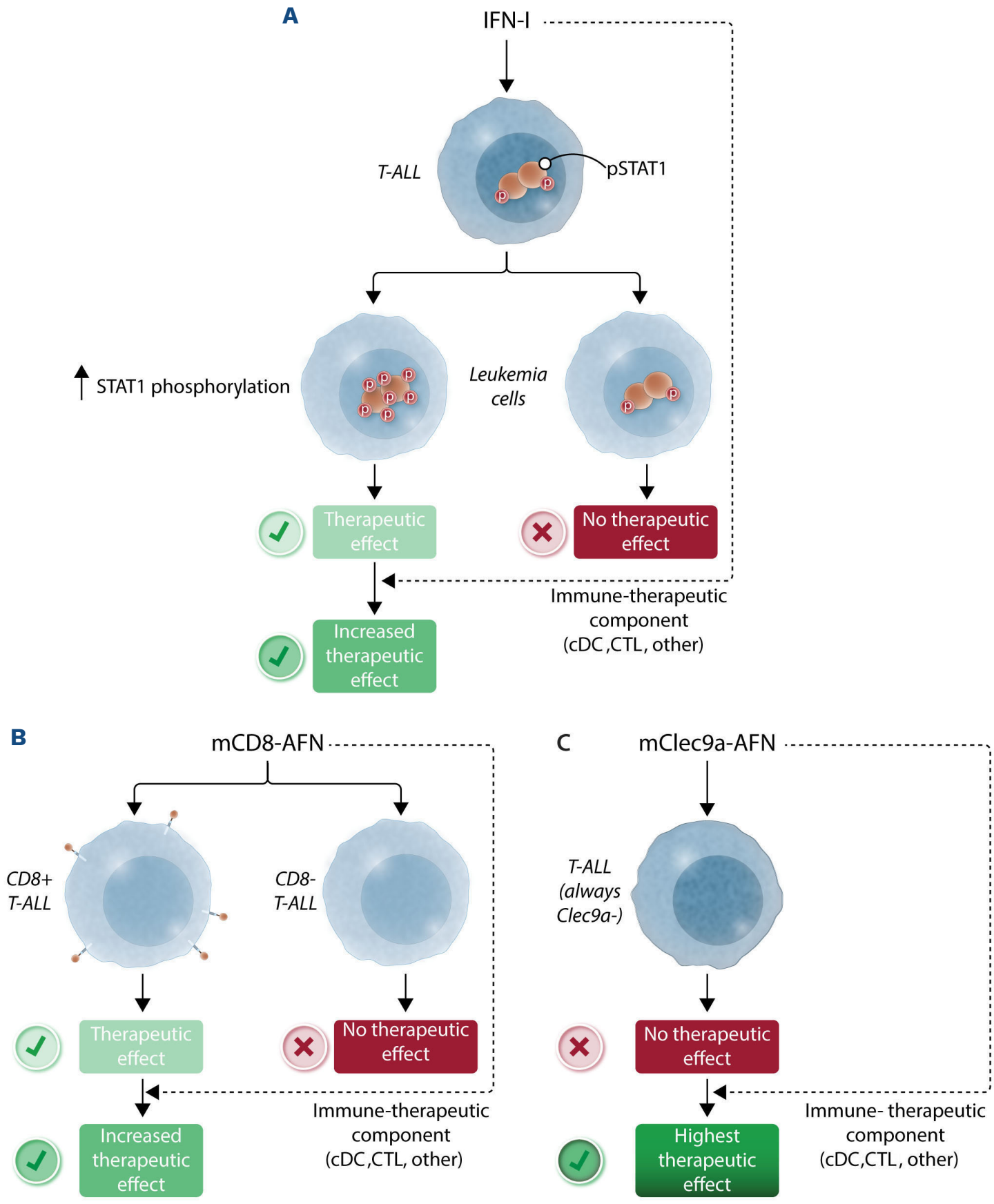

Figure 1. Direct and indirect antileukemic effects of different interferon treatments. (A) Effects of IFN-I treatment. (B) Effects of IFN-I treatment targeted to CD8⁺ cells using AcTaferons (mCD8-AFN). (C) Effects of IFN-I treatment targeted to Clec9a⁺ cells using AcTaferons (mClec9a-AFN). IFN-1: type-1 interferons; T-ALL: T-cell acute lymphoblastic leukemia: cDC: classical dendritic cells; CTL: cytotoxic lymphocytes; AFN: activity-on-target interferons.

mClec9a-AFN, or that a different Clec9a⁺ hematologic population might be more relevant in order to mediate the therapeutic effects observed. Related to this, it would be interesting to test the potential synergistic effects of mCD8-AFN and mClec9a-AFN when used concomitantly to treat CD8⁺ leukemias. Further research is therefore warranted to uncover the biological reasons for these differences. Regardless, the important findings of Goossens and colleagues serve to revitalize the field of interferons for the treatment of T-cell malignancies, as AFN show significantly reduced side effects as compared to interferon itself, and both mCD8-AFN and mClec9a-AFN showed direct and/or indirect antileukemic properties which could be exploited for the treatment of interferon-sensitive leukemias alone or in combination with classical chemotherapy regimens which, in turn, might help to reduce or prevent relapses in these patients.

Disclosures

No conflicts of interest to disclose.

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