Chronic myeloid leukemia stem cell biology and interferon α

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A B S T R A C T

Evidence from recent imatinib discontinuation studies suggests that only some patients can maintain remission after cessation of ABL-tyrosine kinase inhibitor (TKI) therapy. This is probably due to the failure of imatinib or second-generation TKI to eradicate primitive chronic myeloid leukemia (CML) stem cells. Interferon α (IFN) currently re-emerges as a combination partner for TKI, because recent evidence implies that IFN can increase the depth of TKI-induced molecular remission and also the number of patients with undetectable minimal residual disease (UMRD). UMRD has been defined as a prerequisite for potential suitability for TKI discontinuation studies. Based also on different modes of action, a TKI / IFN drug combination may thus hold promise of maximizing the number of patients who can permanently stop any drug therapy.

Learning goals

At the conclusion of this activity, participants should be able to:
- describe current understanding of CML stem cells;
- reflect CML persistence as an unmet treatment need in the era of TKI;
- distinguish features of remission induction by interferon α and ABL-specific kinase inhibitors;
- propose rationales for imatinib / interferon alpha combination therapy in CML patients.

Introduction

With the introduction of BCR-ABL kinase inhibitors, chronic myeloid leukemia (CML) has become a rather indolent type of leukemia. The overall survival of CML patients is close to 90% after eight years, and emergence of TKI resistance and progression into accelerated phase and blast crisis is exceedingly rare if patients achieve respective response milestones according to European LeukemiaNet (ELN) guidelines.[1] However, CML stem cells are resistant to TKI and life-long treatment is important to sustain remission and prevent progression. This comes at the expense of side-effects, potential long-term toxicities and extremely high costs.

Unraveling the mechanisms of CML stem cell persistence is a prerequisite to develop new strategies that may ultimately convert an infinite into a transient form of therapy. This is an ambitious challenge, because residual CML stem cells closely resemble their normal counterparts, which would explain why an efficient targeting of biological, biochemical or genetic differences between CML and normal stem cells is so difficult.[2] Pre-clinical data, including those from CML animal models, have uncovered numerous novel drug candidates for this purpose,[3] but for a variety of reasons none of these have so far entered advanced stages of clinical development. In the light of these facts, it may perhaps not come as a surprise that a relatively out-dated substance, interferon alpha 2a or 2b (IFN), whose mode of action in CML is, at best, only vaguely understood, is currently being tested in clinical trials as a combination partner for TKI. This IFN revival is reasonable mainly for three reasons. First, IFN / imatinib combination therapy was shown to be significantly more efficient than imatinib monotherapy in inducing molecular end points.[4-8] Secondly, combining low doses of pegylated IFN (pegIFN) with imatinib is clinically feasible and effective.[9] Finally, based on different effector mechanisms, this combination may hold the promise of also targeting CML stem cell persistence. Therefore, I will briefly summarize key CML stem cell characteristics and highlight those that govern imatinib / TKI insensitivity.

CML stem cells: features governing imatinib response

Although BCR-ABL is the causative oncogene of CML,[10,11] it is comparably weakly transforming. As opposed to oncogenes such as MOZ-TIF or MLL-AF9, expression of BCR-ABL does not directly confer self-renewal ability to committed progenitor cells.[12-14] CML leukemogenesis must, therefore, involve expression of BCR-ABL in the context of a hematopoietic stem cell providing intrinsic self-renewal capacity. Moreover, recent evidence suggests that BCR-ABL^{p210} when expressed from the endogenous promoter in the *Bcr*-locus is incapable of inducing CML.[15] This observation would be in line with the finding that BCR-ABL mRNA can frequently be detected in healthy donors who will

never develop CML.[16,17] It also supports the model that a fully malignant, disease-perpetuating CML stem cell clone only emerges over time, starting from a pre-malignant, BCR-ABL-positive stem cell by a sequential accumulation of additional genetic and / or epigenetic changes.[18]

Clinical observations, and particularly imatinib discontinuation studies, provided extremely valuable insights into the biology of persisting CML stem cells. They are considered to be a small BCR-ABL-positive population which resides in the $CD34^+/CD38^-/CD90^+$/lineage-[19] or a CD34-/lin- stem cell compartment.[20] However, in contrast to numerous *in vitro* studies, which so far mainly imply a relatively homogenous TKI insensitivity of the entire CD34+/$CD38^-$ stem cell fraction,[21-24] longitudinal *in vivo* data from CML patients under imatinib or dasatinib treatment provide intriguing new insights. Accordingly, both the $CD34^+/CD38^+$, but particularly also the $CD34^+/CD38^-$compartment (enriching for stem cells), are *in vivo* very rapidly cleared from Philadelphia chromosome-positive leukemic cells.[25] Therefore, it seems justified to propose that only a very minor fraction of $CD34^+/CD38^-$ CML stem cells are capable of sustaining long-term survival in a BCR-ABL-kinase independent manner (Table 1).

Under circumstances of permanent kinase inhibition (with imatinib or any other TKI), residual CML stem cells are apparently genetically quite stable. This is evidenced by a lack of progression or of TKI resistance development once a deep molecular remission has been achieved.[26-28] However, if kinase activity is restored upon imatinib cessation, persisting CML stem cells are capable of fully reconstituting frank CML within weeks or months. Why a minute fraction of stem cells escape imatinib's selective pressure is still not completely understood. Various genes and pathways (e.g. Foxo, Wnt/catenin, AKT/mTor, JAK2, ALOX5, SIRT1, PP2A, BCL6 / p53, NFAT, Hedgehog and cytokines such as SDF, PTH, GM-CSF) or external stimuli by the stem cell niche have been associated with CML stem cell persistence. Most of these candidates have been derived from CML mouse models and were confirmed *in vivo* as reasonable therapeutic targets to overcome persistence.[3] However, a detailed description of them would be beyond the scope of this paper (for further review see O'Hare *et al*.[2] and Chomel and Turhan[29]).

Table 1 summarizes clinical and therapeutic implications of human CML stem cell characteristics that govern the biology of imatinib persistence and may be also relevant targets of IFN signaling.

IFN-signaling

How interferon works: the IFN signaling pathway

Interferon has come of age. After the first discovery of interferon in 1957, diverse interferon proteins have been identified and were classified as type 1 interferon (a,b), type 2 interferon (γ) and type 3 interferon (IFN γ1-3).[53] Only the type 1 interferon, IFN, and IFN signaling is briefly presented here, as it is relevant for CML therapy.

In short, IFN binds to the type 1 IFN receptor subunits, IFNAR1 and IFNAR2, on the cell surface of hematopoietic cells. The latter are associated with Janus activated kinase 1 (JAK-1) and tyrosine kinase 2 (Tyk2) (Figure 1). Upon ligand binding, JAK-1 and Tyk2 become phosphorylated and in turn activate signal transducer and activator of transcription (STAT) proteins, mainly STAT1, STAT2, but also STAT3 and STAT5.[54-56] Phosphorylated (activated) STAT1 and STAT2 form a complex with unphosphorylated IRF9 to build the ISGF3 complex, which translocates into the nucleus and initiates transcription of interferon sensitive genes (ISG) by binding to specific sites in their promoters, such as the interferon stimulated response (ISREs) or gamma interferon activation site (GAS)-elements (Figure 1). Which ISG become activated upon IFN binding to mediate apoptosis, cell cycle control, target gene transcription[57] or immune modulatory effects depends on a multitude of factors that cannot be elucidated in great detail here. Interferome v.2.0 provides a useful platform to search for a microarray database for cell type specific target genes activated by interferons in different species *in vivo* or *in vitro*.[58]

Table 1. Features of CML stem cells that govern biology of imatinib response and CML persistence.

Features of CML stem cells (governing imatinib biology)	Clinical / therapeutic consequence
BCR-ABL kinase activity is potently inhibited by TKI[30,31]	TKI prevent CML progression and improve survival[1,32] BCR-ABL-dependent expression of tumor-associated antigens may restrict anti-leukemic immune responses[33,34]
Lack of BCR-ABL addiction[22,23,30,35]	Indefinite TKI treatment of CML1 CML relapse after TKI discontinuation[36-39] CML stem cell persistence[21,39-41] Lack of genetic pressure to select for kinase mutations and absence of *de novo* TKI resistance development during deep molecular remission[26,27] Failure of second-generation TKI to overcome stem cell persistence BCR-ABL independent survival pathways as targets to overcome persistence[29]
Acquisition of self-renewal in progenitors during CML progression[42,43]	Low therapeutic efficacy of TKI during AP/BC
High BCR-ABL expression at primary diagnosis[22,23,44,45]	Rapid upfront elimination of BCR-ABL over-expressing clones may restrict progression[46,47]
Low BCR-ABL expression during persistence[41,48]	CML persistence mechanism[41,49] Maintenance of low level oncogene (BCR-ABL) activity is tumor suppressive[50-52] Freedom from progression[26,27] and increased overall survival as a consequence of deep molecular remission[28]

Besides activating signaling via the JAK-STAT pathway, the IFNAR signaling network is further enriched by feeding alternative pathways such as PI3K-Akt-mTor,[59,60] MAP kinase (including erk and p38-MAPK),[61] C3G-Rap-1[62] or CrkL-STAT5[63,64] (reviewed by Platanias[54]) in a JAK-STAT-independent manner (Figure 1). The outcome of any of these signaling activities depends on the respective cell type and differentiation status (primitive stem cells, immature progenitor cells, differentiated immune cells) and concurrent signaling input from other pathways. In CML, the situation is further complicated by the presence of BCR-ABL, because aberrant BCR-ABL signaling interferes with all of the aforementioned IFN-employed pathways with a hardly predictable outcome.

Clinical activity of IFN in CML

Conventional IFN

The first *in vitro* reports linking IFN with inhibitory effects on hematopoietic progenitor cell proliferation were published over four decades ago.[65-67] It was subsequently noted that IFN also had clinical activity in the treatment of neoplasia, namely, breast cancer, multiple myeloma and lymphoma.[68] This stimulated the further clinical development of IFN in CML.[69-72] These early trials revealed an unprecedented CML treatment efficacy for IFN. Rates of hematologic complete remission (CHR) with IFN monotherapy ranged between 22% and 71%.[69,70,73] Other studies report that 10-30% of patients achieved a complete cytogenetic remission (CCyR) with IFN.[74-77]

The 5-year overall survival with IFN was 50-59% and compared favorably with the overall survival (OS) of 29-44% for patients receiving busulfan or hydroxyurea.[74-77] In an analysis of 1573 IFN-treated patients, the median survival with IFN was 8.2 years for low-risk patients, 5.4 years for intermediate-risk patients, and 3.5 years for high-risk patients.[78]

CCyR has been established as a reliable predictor for good long-term prognosis. In a European study of 317 CCyR patients under IFN (IFN-CCyR), the OS after ten years was 72%. It was 89% for a Sokal low-risk cohort.[79] These data were corroborated by another study on 512 patients, of whom 140 (27%) achieved a CCyR with IFN. In this study, the OS was 78% after ten years.[80] Two controlled trials suggested that a combination of IFN with chemotherapy (cytarabine and hydroxyurea) increases survival.[81,82] Before imatinib became standard therapy, IFNa plus cytarabine was considered the standard of care for

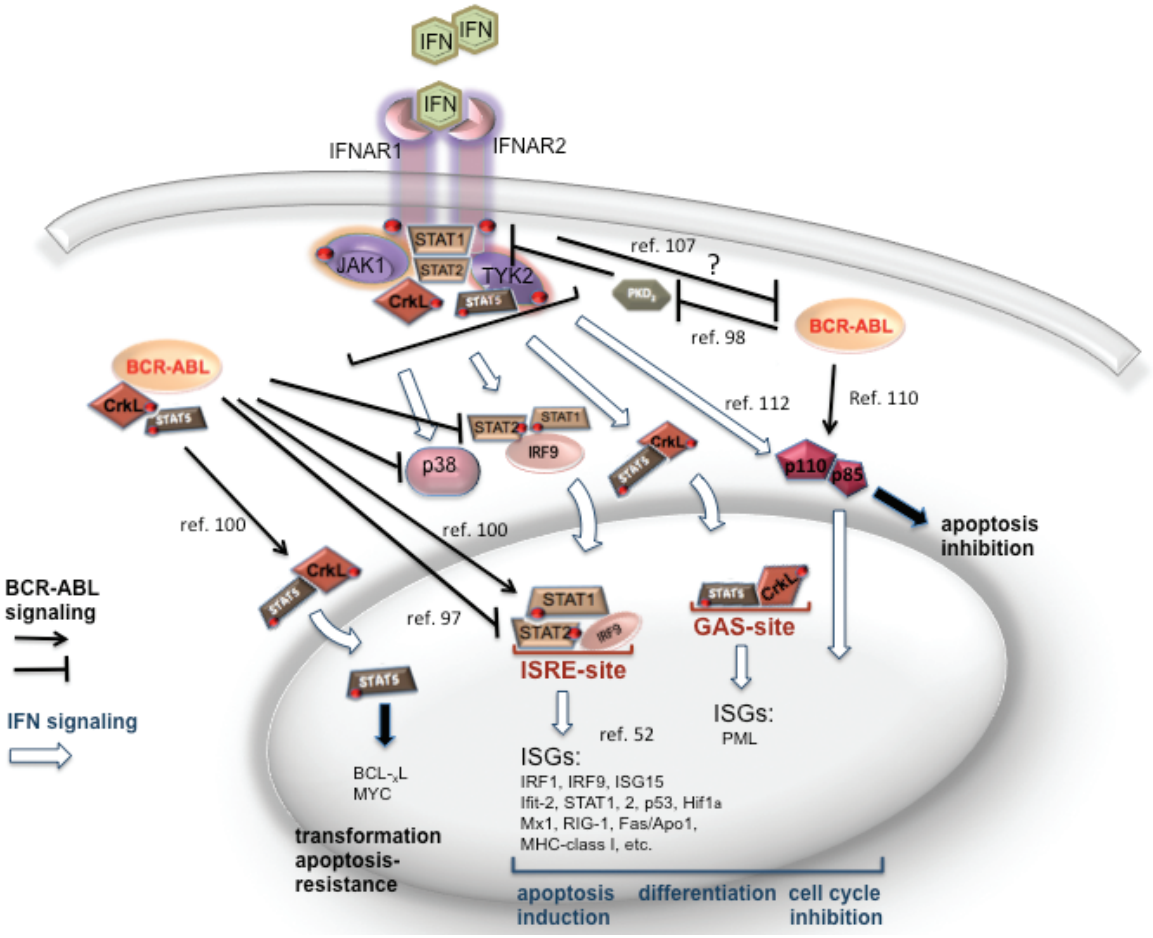

Figure 1. Cross-interference between BCR-ABL- and IFN- signaling cascades and possible biological effects. Of note, inhibition of BCR-ABL with imatinib or second-generation tyrosine kinase inhibitor (TKI) would restore IFN-initiated physiological signaling flux and thus mechanistically explain a TKI / IFN treatment synergism.

CML patients that could not undergo allogeneic stem cell transplantation.[81]

Pegylated IFN

Pegylated IFN formulations were developed to increase IFN exposure through a linear pharmakokinetic profile and to limit side-effects. Whereas a phase I study indeed suggested that pegylated IFN 2b induces improved response rates compared to conventional IFN 2b, 2 controlled trials comparing IFN 2a with PegIFN 2a[83] and IFN 2b with PegIFN 2b[84] gave inconsistent results. Nevertheless, based on the results of the Lipton study, in which PegIFN 2a nearly doubled the rates of major cytogenetic responses compared to standard IFN,[83] and the convincing data from the French and Nordic imatinib / IFN combination therapy trials,[4,5] pegylated IFN is the preferred IFN drug.

Comparing features of IFN and imatinib responses

Mechanisms and kinetics

Tyrosine kinase inhibitors, such as imatinib, specifically inhibit the causal oncogenic kinase of CML BCR-ABL. This results in proliferation arrest and apoptosis of the Ph-positive (Ph^+) clone. Responses occur fast. In the IRIS study, 84% of the imatinib-treated patients, but only 30.3% of the IFN-treated patients achieved a major cytogenetic response after 12 months.[85] CCyR rates at 18 months were 76.2% in the imatinib group and 14.5% in the group that was given IFN.[85] If a CCyR was achieved, the median time until CCyR was approximately 16 months with IFN.[80] Thus, responses to IFN occur rather slowly. In contrast to imatinib, a myriad of possible effector mechanisms are initiated by IFN signaling (Figure 1) including pro-differentiating, cell cycle inhibitory and direct cytotoxic effects. However, also cytokine and complex immune regulatory effects are supposedly involved in IFN induced remission.[77,86,87]

Durability

Imatinib-induced CCyRs are also more durable than those achieved with IFN. For example, according to a European registry study, loss of a CCyR occurs with IFN at a rate of 12% annually within the first two years. The probability of a CCyR-loss after five and eight years was 42% and 50%, respectively.[79] Although imatinib patients may also lose their CCyR, these events (loss of cytogenetic remission) are dramatically less frequent. Progressions in the IRIS study were documented at a rate of 5.1% in the first year *versus* only 0.3% in the fourth year of therapy.[88]

Depth of remission

The depth of molecular remission with imatinib and newer TKI steadily increases over time. After eight years of imatinib therapy, 36.5% and 46% of the patients may obtain a MR4.5[28,89] also referred to as UMRD (undetectable minimal residual disease). Comparable molecular remission data are rare for IFN CCyR patients. In the IRIS study, it was estimated that 39% had a 3-log decline in BCR-ABL transcript levels from baseline, as compared with only 2% in the IFN cohort.[90] This suggests a significant inferiority of IFN in the induction of molecular remissions. In an earlier study of IFN-CCyR patients, the median BCR-ABL/ABL ratio was 0.04%.[91] Although difficult to compare with current BCR-ABL PCR standards, this depth of remission would be roughly equivalent to an MR3 or MR4. BCR-ABL-positive MRD was evident in all of 54 tested IFN-CCyR patients.[92] This altogether supports the notion that TKI have a significantly higher potency in inducing and maintaining sustained and deep molecular remissions.

Quality

A unique hallmark of IFN-based remissions is that IFN can occasionally be successfully discontinued irrespective of the detectability of Ph^+ or $BCR\text{-}ABL^+$ minimal residual disease.[7,79,92,93] However, chances of remaining relapse free directly correlated with remission depth (e.g. BCR-ABL/ABL ratio <0.045%) and CCyR duration. In contrast, none of the imatinib discontinuations that were carried out in patients with detectable BCR-ABL mRNA, i.e. MRD greater than MR4.5, have been successful. Discontinuation of imatinib therapy in these patients unequivocally led to relapse.[94,95] Even the majority (approx. 60%) of patients in whom imatinib is discontinued after having obtained undetectable BCR-ABL mRNA level subsequently relapse.[36-39]

In conclusion, imatinib treatment efficacy is strong, but is strictly dependent on a permanent drug exposure. In contrast, IFN induction of molecular remission is poor, but such remissions can sometimes be maintained irrespective of further IFN exposure if the MRD level is low.

Supposed mechanisms of cooperativity between IFN and imatinib

Three prospective trials have suggested that a combination of pegIFN and imatinib significantly increases rates of deep molecular remission when compared to imatinib alone.[4,5,8]

Furthermore, imatinib discontinuation trials[37-39,89] revealed an association between a previous IFN therapy and the chance of remaining relapse-free after stopping imatinib. Neither the duration of UMRD before imatinib cessation, nor the persistence of BCR-ABL DNA predicted relapse.[39] It was concluded that a superior, IFN-induced, immunological control might be involved in preventing relapse in these patients. This view reflects the classical understanding of an IFN-mediated, immune stimulatory anti-CML activity. Non-exclusive, alternative mechanisms of IFN involve effects on CML cell proliferation, cell cycle, and differentiation (Figure 1).

IFN-induced anti-leukemic immunity

The physiological function of IFN is to elicit antiviral immune responses. In CML, distinct immune-modulatory effects such as NK- and $\gamma\delta^+$T-cell expansion have been linked with sustained treatment responses to IFN.[96] Moreover, there is evidence that IFN elicits anti-leukemic cytotoxic T-cell (CTL) responses.[67,97] These CTL specifically recognize various leukemia-associated antigens on CML cells such as proteinase 3, WT-1, hTERT or myeloperoxidase.[98]

Evidence supporting a role for proteinase 3 specific CTL in mediating anti-leukemic immune response is provided by the finding that only IFN responders harbor proteinase 3-specific CTL.[34,98-100] As exemplified by proteinase 3-specific (PR1)-CTL in CML, the size and repertoire of anti-leukemic CTL clones underlies permanent shaping.[100] A main determinant of this process is the leukemia mass. High and low avidity PR-1 CTL have been found in CML patients. Only high avidity CTL kill target cells very efficiently. They presumably emerge when the circulating antigen load is low.[100,101] This would predict that TKI therapy, which dramatically reduces leukemia mass, favors the emergence of high avidity CTL. TKI would thus augment the potency of IFN to elicit highly efficient CTL responses.

On the contrary, shutting off BCR-ABL kinase activity during TKI/IFN therapy may inhibit immunogenicity and limit CTL responses.[33,102] This would explain why imatinib patients have lower numbers of circulating PR1-CTL than IFN-treated patients.[34] Consequently, a TKI/IFN combination therapy should be followed by an IFN maintenance period in absence of BCR-ABL kinase inhibition in order to boost target cell recognition. This is currently tested in the ongoing CML-V study (EudraCT, n. 2010-024262-22).

Immune-independent anti-leukemic effects of IFN on CML progenitor and stem cells

First of all, data from the SPIRIT and Nordic pegIFN / imatinib combination therapy trials[4,5] support the existence of direct cytotoxic effects of IFN when given in the context of imatinib. This conclusion is based on data from the Nordic trial. The 12-month MMR rates were already superior for pegIFN / imatinib if pegIFN was given for at least three months. Surprisingly, a longer exposure (> 6 months) did not even further increase MMR rates at 52 weeks.[5] Likewise, although 46% of the patients in the SPIRIT study had stopped pegIFN within the first year, MMR responses at the 12-month landmark were still significantly more frequent in the pegIFN / imatinib cohort. These data suggest that a short-term exposure to IFN is sufficient to induce a treatment synergism with imatinib. This does not evidently rule out that immune effects are also involved. However, based on the rapid kinetics of response and the low cumulative doses of IFN used, a direct synergism between IFN and imatinib at the progenitor level seems to be more likely than an acute elicitation of immune responses. This conclusion is also supported by *in vitro* studies. IFN, but not imatinib preferentially inhibits survival of primitive CML long-term culture initiating cells (LTC-IC). In turn, imatinib, but to a lesser extent IFN, inhibits colony formation of committed progenitor cells.[103] This would imply that the high speed of molecular remission induction involves dual targeting of CML hematopoiesis on the level of primitive CML stem, but also more committed progenitor cells.

Inhibition of BCR-ABL may enable restoration of IFN signaling

Constitutive BCR-ABL signaling interferes with multiple, if not all, of the IFN signaling pathways[104-111] (Figure 1). As a result, members of the IFN signaling cascade (e.g. IFNAR, STAT5, CRKL, Rac1-p38, PI3K-AKT-mTOR etc.) are constitutively exploited (inhibited or activated) (Table 2) and the physiological IFN signaling outcome such as growth inhibition, proliferation, differentiation, or apoptosis[53-56] is altered by BCR-ABL (Figure 1). This is exemplified by the Rac1/p38MAPK pathway, a well documented IFN response pathway mediating anti-proliferative effects in normal[54] and IFN-responsive CML cells.[61] BCR-ABL inhibits p38 expression and activation and thus blunts IFN responsiveness.[110,111] BCR-ABL inhibition with imatinib restores apoptosis sensitivity in a p38-kinase

Table 2. Interference between BCR-ABL and IFN signaling pathways. Note: common signaling targets of IFN and BCR-ABL are in part regulated by both IFN or BCR-ABL (activation), but frequently induce a divergent biological outcome. Inhibition of BCR-ABL-signaling by TKI may restore the physiological IFN response, providing a rationale for synergism between TKI and IFN treatment.

Upstream regulator	**BCR-ABL**		**IFN**	
Target molecule in CML cells	**Biochemical effect**	**Biological consequence**	**Biochemical effect**	**Biological consequence**
IFN receptor (IFNAR)	IFNAR degradation105	loss of IFN responsiveness	receptor and pathway activation[56]	growth arrest differentiation apoptosis[53,54,56]
BCR-ABL	-	-	mRNA suppression[112] no mRNA regulation[113]	growth inhibition[112]
CRKL- STAT-5	RKL-STAT5 complex formation[99]	transformation and apoptosis resistance via MYC and BCL-$_x$L [106]	CRKL-STAT5 complex formation[63,64]	growth inhibition[114] via ISGs
STAT-1 and STAT-3 STAT1, 3, 5	inhibition of IFN-induced phosphorylation activation[107]	reversal of IFN dependent growth inhibition104 transformation	activation[53,54,56]	stem cell cycling[119] or growth arrest[54]
C3G RAP-1	activation	BCR-ABL oncogene addiction, proliferation, apoptosis resistance[108,109]	transient activation[54,62]	anti-proliferative responses via p38?
PI3K-Akt-mTor	activation	transformation and apoptosis resistance[115,116]	activation[54,59]	pro- and anti-apoptotic responses[54,117]
Rac1-p38-MAPK	inhibition of p38 expression and activity[110,111]	loss of IFN response and apoptosis sensitivity to imatinib[104,111]	activation (phosphorylation)	p38 dependent growth inhibition[61,118]

dependent manner.[111]

It has recently been shown that IFN induces cell cycle entry of normal stem cells in mice[119,120] thereby sensitizing them to undergo apoptosis in response to chemotherapy.[119] It was suggested that imatinib may also be able to kill CML stem cells if IFN would induce cell cycle entry of leukemic stem cells. However, the experimental evidence to support this model in CML is still lacking.

Figure 1 summarizes the interference of BCR-ABL and physiological IFN signaling on various signaling levels, starting with the expression of the IFNAR. A restoration of IFN signaling by BCR-ABL inhibition could explain in part the synergism between imatinib and IFN therapy and why in combination with imatinib only low doses of IFN may be sufficient to achieve the therapeutic effects.

Summary and Conclusions

Ever since the discovery of donor lymphocyte infusions (DLI) as curative procedure in relapsing patients after allogeneic stem cell transplantation,[121] it became clear that immune cells are capable of curing CML. IFN employs and stimulates autologous immune effector cells, including T cells, to elicit autologous anti-leukemic immune responses in CML.

In contrast, TKI rapidly kill Ph+ mature and primitive hematopoietic cells, but leave behind a tiny (and poorly characterized) fraction of "CML stem cells". These cells show BCR-ABL-independent long-term survival and are perceived as the source of relapse in CML patients who discontinue TKI therapy.

Recent clinical studies have now demonstrated that immune-modulatory and cell-signaling effects of IFN potently synergize with TKI, which is reflected by the achievement of a significantly superior molecular remission depth. Based on this and preliminary clinical observations, the IFN/TKI combination holds promise for increasing the number of patients who can successfully discontinue TKI therapy.

After 2000, most clinicians said "goodbye" to IFN because the data with imatinib just looked so good. But some "IFN people" (including our group) kept on looking for a role for IFN even in the era of TKI. As a result, now, 12-13 years later, we are seeing some interesting and previously unpredictable data that really justify further study of the combination. From a personal point of view, it appears to be an ironic twist of fate that 'dusty' IFN, previously conquered by imatinib, currently returns to 'fix' the 'stem cell weakness' of imatinib itself. Indeed, if ongoing and future IFN / TKI combination trials such as "Nilo-Peg" in France or the big German "TIGER" study, which are prospectively investigating the value of adding IFN to nilotinib with regard to molecular remission and discontinuation end points turn out positive, not losing interest on IFN in CML has definitively been worth its while.

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