Molecular pathways: BCR-ABL

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Abstract

Aberrant Tyrosine kinase (TK) activity is critical in many hematological disorders, including chronic myeloid leukemia (CML) characterized by the constitutive activity of BCR-ABL. ABL therefore represented a crucial target for new therapeutic strategies. The molecular pathways abnormally activated by the oncoprotein are summarized and they may represent additional opportunities to develop new drugs to overcome the resistance to TK inhibitors. Among them the PI3K/Akt pathway can be effectively blocked by mTOR inhibitors, or RAS pathway, resulting MEK1/2 and MAPK activation can be targeted. Furthermore, mitotic kinases can be blocked by Aurora kinase inhibitors or Pim kinases by selective serine-threonine kinase inhibitors. Finally, the abnormal pathways sustaining the self renewal of leukemic stem cells are described as possible targets to completely eradicate the leukemic clone including Hedgehog pathway which can be blocked by Smo inhibitors and CXCR4/SDF1 axis which can be targeted by specific antagonists.

Background

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder characterized by the Philadelphia (Ph) chromosome, which results from the t(9;22)(q34;q11) balanced reciprocal translocation.\(^1\) The molecular consequence of the Ph chromosome is the generation of the BCR-ABL oncogene that encodes for the chimeric BCR-ABL oncoprotein, with constitutive kinase activity that promotes the growth advantage of leukemic cells.\(^2\) The deregulated tyrosine kinase activity of BCR-ABL has been demonstrated to be necessary and sufficient to maintain leukemia phenotype of CML.\(^3\) The activation of the ABL tyrosine kinase represents a primary event in the genesis of CML as demonstrated by the retrovirally mediated insertion of a human BCR-ABL gene into murine hematopoietic stem cells and the creation of BCR-ABL transgenic mice.\(^3\) This represents a critical issue in the view of designing molecular therapies.
The BCR-ABL oncogenic pathway

The ABL protein physiologically shuttles between the nucleus and the cytoplasm, however, when fused to BCR, the oncoprotein loses this property and it is mainly retained within the cytoplasm where it interacts with the majority of proteins involved in the oncogenic pathway. ABL tyrosine kinase activity is constitutively activated by the juxtaposition of BCR so favouring dimerization or tetramerization and the subsequent autophosphorylation. This increases the number of the phosphotyrosine residues on BCR-ABL and, as a consequence, the binding sites for the SH2 domains of other proteins.6-7

The abnormal interactions between the BCR-ABL oncoprotein and other cytoplasmic molecules leads to the disruption of key cellular processes. Some examples could be represented by the perturbation of the Ras-MAP kinase leading to increased proliferation, of the JAK-STAT pathway leading to impaired transcriptional activity and of the PI3K/Akt pathway resulting in increased apoptosis.8 The aminoterminal BCR-encoded sequences of BCR-ABL contain a tyrosine-phosphorylated site that binds the SH2 domain of the adaptor protein Grb2.6 It is now evident that the phosphorylation of BCR Tyr177 is essential for BCR-ABL mediated leukemogenesis9 and its mutation largely abolishes GRB2 binding and diminishes BCR-ABL induced Ras activation.7

This latter results from interaction of BCR-ABL with other cytoplasmic proteins, which function as adaptor molecules, thus creating multiprotein signalling complexes. The BCR-ABL Grb2 complex recruits Sos, (Son of Sevenless), which is constitutively associated with the Grb2 SH3 domain.10 In turn, the BCR-ABL-Grb2-Sos complex stimulates conversion of the inactive GDP-bound form of Ras to its active GTP-bound state11 and the activation of the scaffold adapter GRB2-associated binding protein 2 (GAB2).12 As a consequence, GRB2/GAB2/SOS complex causes constitutive activation of RAS downstream pathway so activating MEK1/2 and MAPK proteins causing, as a final result, an abnormal cell proliferation. In addition this complex activates the phosphatidylinositol 3-kinase (PI3K)/AKT pathway.13 (figure 1) which promotes survival by
suppressing the activity of forkhead O (FOXO) transcription factor, enhance cell proliferation by inducing p27 proteosomal degradation and by mTOR activation.

In addition BCR-ABL, through PI3K/AKT/FOXO4 and finally through upregulation of mTOR potently blocks an important cellular process such as autophagy. BCR-ABL may activate PI3K by more than one pathway, since also Crk and Crkl have been shown to connect BCR-ABL with PI3K. Once activated, PI3K activates Akt kinase which represents a key downstream effector by exerting many cellular effects through the phosphorylation of downstream substrates including Bad, caspase 9, Mdm2 and Ask1 that regulate the apoptotic machinery, therefore resulting into prolonged survival and expansion of the abnormal clone.

Key transcription factors are involved in BCR-ABL signalling. Among them a key role is played by STAT1 and STAT5 (signal transducer and activation of transcription) which are constantly active in BCR-ABL positive cell lines and in primary cells from CML patients contributing in the induction of cytokine independence.

In normal cells, nuclear translocation of STATs occurs exclusively after cytokine binding to receptors and is mediated by activation of the receptor-associated JAK kinases. By contrast in CML STATs seem to be activated in a JAK independent manner, through a direct association of STATs SH2 domains with phosphorylated tyrosines on BCR-ABL. Activation of STAT5 is, at least partially, responsible for protection from programmed cell death through the upregulation of the antiapoptotic molecule BCL-xL together with the inactivation of the proapoptotic molecule BAD by AKT.

Another postulated nuclear ‘target’ of the transforming activity of the BCR-ABL protein is represented by the protooncogene MYC, which is expressed at a high level in CML cells. MYC activation, however, seems to be independent from RAS pathway but it seems to be directly upregualted by ABL SH2 region. There are several lines of evidence showing that Myc is often overexpressed in blast crisis compared with chronic phase, so linking MYC to progression. In
vitro inhibition of c-Myc with antisense oligonucleotides or dominant-negative constructs can inhibit BCR-ABL transformation or leukemogenesis.\textsuperscript{19}

All reported activated signalling pathways converge into a unique terminal point: loss of control of proliferation and expansion of the leukemic clone. Any effort in the understanding of the precise definition of the relative contribution of each signal transduction pathway to the leukemic process is an important area of research because the combination of a tyrosine kinase inhibitor together with a downstream inhibitor, may represent a further clinically successful strategy.

Despite the seemingly endless expansion of the list of pathways activated by BCR-ABL and the increasing complexity that is being revealed in these pathways, all of the transforming functions of BCR-ABL seem to be dependent on its tyrosine kinase activity.\textsuperscript{20} This precondition has an incredible intrinsic clinical potential in view of a more and more sophisticated targeted therapy.

Clinical-Translational Advances

Kinase inhibitors

Imatinib, a small molecule tyrosine kinase inhibitor (TKI), was the first drug to be developed that was able to directly target BCR-ABL tyrosine kinase activity and to be tested in CML.\textsuperscript{21} In a short time it has become the standard frontline therapy for all CML patients in early chronic phase (CP) based on the response rates and the good tolerability demonstrated.\textsuperscript{22}

Despite the exciting results obtained with imatinib, after 8 years of follow-up the cumulative complete cytogenetic response (CCyR) rate for first-line imatinib treated patients was 83\%, the event-free survival (EFS) rate was 81\%, and the estimated overall survival (OS) rate 85\%.

However, it should be considered that if the CCyR is not achieved after 12 months of imatinib therapy, the probability of progression or loss of response raise to 38\%. Indeed, after 8 years of follow-up, it was assessed that early cytogenetic response is predictive of long-term outcome: the cytogenetic response is therefore considered a prognostic indicators of lack of events, whereas non-optimal responders had poorer prognosis.\textsuperscript{23} In addition, the degree of response is critical. The IRIS
study also confirmed that the achievement of major molecular response (MMR) at 12 months predicts a low risk of events or progression thus emphasizing the value of achieving a molecular response early during treatment.

Basing on these data it appeared clear that for at least one third of patients, the potential exists to improve on what can be achieved with standard imatinib 400 mg treatment. It was therefore investigated the possibility of inhibiting BCR-ABL activity in a more potent manner in order to improve the results of first line therapy. Therapeutic strategies assessed include modified imatinib-based regimens and first-line administration of next-generation TKIs.

Several highly potent next-generation BCR-ABL inhibitors have been developed as strategies to overcome imatinib resistance and improve the prognosis of patients with CML. These include novel and more potent multi-TKIs such as dasatinib (Sprycel; BMS-354825, Bristol-Myers Squibb, New York, NY), an orally bioavailable dual BCR-ABL and Src inhibitor, and potent selective BCR-ABL inhibitors such as nilotinib (Tasigna; AMN-107, Novartis, Basel, Switzerland). Both nilotinib and dasatinib induced significant clinical responses. Dasatinib blocks BCR-ABL at low concentration but it is less selective than imatinib. As imatinib it inhibits BCR-ABL, Kit and PDGFR but it blocks also Src kinases, Tec kinases, Eph kinases and many others. Nilotinib blocks BCR-ABL al low concentration than imainib but it appears more selective than dasatinib maintaining, as imatinib, few tyrosine kinases as targets.

In phase II trials of patients with CP CML, dasatinib and nilotinib were associated with 2-year CCyR rates in imatinib-resistant patients of 45% and 41%.24 Following the impressive results in patients with imatinib failure, dasatinib and nilotinib have been assessed in phase II studies in patients with newly diagnosed CML. The rate of CCyR at 12 months was 80% and the rate of major molecular response was 44% thus showing a superiority compared to imatinib standard treatment with a favorable toxic profile.25 The results of these trials seem to indicate a superior efficacy of the more potent second-generation TKIs with respect to imatinib, particularly in terms of higher rates of CCyR and MMR, that, more importantly, also seem to lead to a decreased number of progressions
of the disease. Although these results still need to be fully evaluated after a longer period of follow-up, the use of next-generation agents in the first-line therapy of CML is likely to become a key area of clinical research during the next few years.

Considering the impressive results obtained with second generation TK inhibitors in front line treatment there are only few fields of intervention we can still envisage in order to optimize the CML cure.

The first is to target what is commonly defined as the Achilles heel which is represented by the emergence of BCR-ABL mutant clones, including T315I which are completely insensitive to the second generation TKIs. Although very rare, this small fraction of patients developing these insensitive clones loose the response and progress during treatment.

An additional step forward compared to the present therapeutic possibilities is represented by the complete eradication of the leukemic stem cells which appear to be resistant to the TK inhibitors so representing a reservoir of the leukemic pool which could eventually favor the reappearance of the disease when TK inhibitors are stopped.

Although very rare, resistant patients at least in the majority of the cases, present mutated clones, particularly aggressive and resistant to the available drugs. Resistance to the BCR-ABL inhibitors may arise from different mechanisms, including BCR-ABL amino acid mutations, gene amplification and mechanisms independent from BCR-ABL.

The T315I mutation at the gatekeeper residue is frequent in advanced phases of the disease and is one of the main cause of resistance, disrupting important contact points between the inhibitors and the enzyme. The complete eradication of the resistant clones could be, at least theoretically faced by making use of two different approaches: for patients developing mutations still sensitive to TKI a more potent inhibition of the TK activity seems to overcome the resistance. This can be obtained by switching to second generation TKs or by increasing imatinib dose. For patients with mutants insensitive to the available drugs a different and more complex approach is required. This is
actually represented by targeting downstream pathways activated by BCR-ABL or by a less selective inhibition of BCR-ABL by drugs blocking multiple kinases including the mutants.

AP24534 (Ponatinib), a potent, orally available multitargeted kinase inhibitor, which is active against pan-BCR-ABL and mutated form and against additional kinases such as VEGFR, FGFR1, PDGFRα and LYN, FLT3. Phase I study demonstrated the tolerability of the drug in all phases of CML as well as in ALL.

A novel TK inhibitor is preclinical phase of development is represented by Deciphera. It belongs to a class of TK inhibitors with the novel mechanism of action since it blocks the switch pocket rather than the ATP pocket. This compound has been demonstrate to inhibit, at least in vitro, all the mutant variants of BCR-ABL.

**Molecular targets downstream of BCR-ABL**

The alternative approach could be represented by targeting molecules downstream of BCR-ABL. One important target is represented by the PI3K/AKT/mTor pathway which is activated by BCR-ABL but also by additional mechanisms, leading to impaired apoptosis of Ph positive cells. (figure 2, panel A)

The mammalian target of rapamycin (mTOR) lies downstream of Akt in the PI3K kinase pathway. It is a serine/threonine kinase made of two complexes, mTORC1 controlling transit from G1 phase to S phase of the cell cycle and mTORC2 which phosphorylates Akt leading to its full activation. Rapamycin (sirolimis, Wyeth-Ayerst Laboratories) has emerged as a potent inhibitor of mTORC signalling. Several rapamycin analogs, CCI-779 RAD-001 and WYE-132 with improved pharmaceutical properties but similar biological effects to rapamycin, are currently undergoing clinical trials. Rapamycin and “rapalogs” are not able to inhibit mRNA translation and protein synthesis in different models of diseases. The direct inhibition of protein synthesis represents a new emerging field of therapy. Therefore small molecules have been developed to target the mTOR kinase domain (Torin1, PP242, and PP30), in order to inhibit both mTORC1 and mTORC2 signaling pathways.
It was shown that BCR-ABL inhibition results into a reactivation of autophagy. This process takes place through inhibition of BCR-ABL/PI3K/AKT/FOXO4/ mTOR pathway. Inhibition of mTor may therefore potentiate imatinib induced autophagy.

In addition, the role of Pim proteins in mediating resistance to mTor inhibition was recently demonstrated. Pim inhibition is therefore an attractive therapeutic approach, especially in combination with PI3K/Akt/mTor inhibition. Pim inhibitors presented high level of in vitro activity and are in preclinical phase of development. Pim inhibitors act by reducing the expression of MYC. In addition, Pim inhibitors results into inhibition of cyclin-dependent kinase 2 activity, presumably regulated by translocation of p27 to the nucleus. It was shown that Pim inhibitors markedly increases the levels of p27, which is consistent with G1 arrest observed after treatment of leukemic cell lines.

Additional selective targets which could be exploited for eliminating the mutant clone are represented by the mitotic kinases. Aurora kinases are a conserved family of serine/threonine kinases that play critical role in the cell cycle. Three members of the Aurora family have been identified: Aurora A, B and C with different localization and functions. Aurora A is primarily associated with the centrosomes and the microtubules in close proximity to the centrosomes beginning in late S-G2 phase. Aurora B acts as a chromosomal passenger protein whose expression peacks at the G2-M transition, with maximum kinase activity in mitosis. Thus far, very few studies addressed the exact role of Aurora C.

The use of antitumor tubulin drugs, such as the Vinca alkaloids and taxanes provided promising results for the treatment of cancer. These drugs, by inhibiting microtubules result in mitotic arrest and cell death. However microtubules are required for adequate molecular transport also in normal cells. This led to the searching for specific targets to obtain a more selective killing of leukemic cells and different Aurora kinase inhibitors have been created. These include hesperadin, MK-0457, ZM447439, MLN8054 and AZD1152. These inhibitors act by blocking the enzymatic
activity by occupying the catalytic ATP binding site.\textsuperscript{41} Many of these compounds resulted effective in inhibiting T315I mutants.

**Stem cell pathways**

An emerging concept in cancer biology is that a rare population of cancer stem cells exists among the heterogeneous cell mass that constitutes a tumor.\textsuperscript{42} This concept applies also to CML. Normal and leukemic hematopoietic stem cell functions are defined by a common set of critical stemness genes that regulate self renewal.\textsuperscript{43} Hematopoietic stem cells (HSCs) and leukemic stem cells (LSCs) share common features: self renewal, the capacity to differentiate, resistance to apoptosis and limitless proliferative potential.\textsuperscript{43} Despite these similarities, several stemness factors, such as Notch, BMI-1, Wnt show differential activation in HSC versus LSC. These differences could therefore be exploited therapeutically.\textsuperscript{44}

It is important to consider that stemness in leukemia is linked to self-renewal. It is extremely likely that LSC undergo self renewal and they are capable of recapitulating leukemia therefore the maintenance of the LSC pool represents a critical factor for the success of any therapeutic intervention. Therefore targeting stemness factors could be the key factor for a successful therapy. HSCs mainly reside in specialized bone marrow microenvironments called HSC niches. The niche provides appropriate signals that maintain the balance between self-renewal and differentiation of stem/progenitor cells. Hedgehog (Hh) is one of the major regulator of cell fate decision. Hh signal is critical for HSC and progenitor differentiation (figure 2, panel B). Hedgehog pathway activation is initiated when Hh ligand binds to Patched (PTCH) which moves away from a second transmembrane protein called Smoothened (Smo). Smo signals to a cytoplasmatic complex that releases a transcription factor (Gli) which translocates to the nucleus where it activates the Hh target genes.\textsuperscript{45} Leukemic cells are believed to rely on autocrine signaling, where Hh ligand, produced by leukemic cells, acts on neighboring leukemic cells to stimulate their growth or survival.
This model is supported by in vitro evidences that that proliferation of tumor cell lines is accelerated by addition of Hh ligand \(^4^6\) and inhibited by the addition of Hh neutralizing antibody or by cyclopamine, a Hh pathway antagonist. Finally Hh acts through a paracrine mechanism as well. Hh ligand secreted by neoplastic cells signals to the microenvironment and the stromal cell compartment signals back to leukemic cells.\(^4^7\)

The clear link between Hh pathway and human leukemias led to identify small molecules to block the pathway. Different classes of small molecule Hh antagonists have been identified through cell based screens using Hh reporter assay. \(^4^5\)

Among the molecules identified CUR61414, an aminoproline Hh antagonist, can block elevated Hh signaling activity resulting from oncogenic mutations within Patched-1 sequence. \(^4^8\) In addition, a novel series of Hh pathway inhibitors, 1-amino-4-benzylphthalazines (Novartis, Institutes for Biomedical Research, Cambridge, Massachusetts) has been identified and confirmed to act via antagonism of the Smo receptor.

WNT-mediated signaling has been shown to regulate cell-fate determination, proliferation, adhesion, migration and polarity during development (figure 2, panel C). In addition to their crucial role in embryogenesis, WNT proteins and their downstream signaling molecules have been implicated in leukemogenesis. Wnt signaling has been implicated in maintaining and amplifying stem cells as well as in defining the stem cell fate. The major effector of the Wnt pathway is $\beta$-catenin. In the absence of Wnt signaling $\beta$-catenin is retain in the cytoplasm through a direct interaction with Axin, APC and GSK3. The phosphorylation of $\beta$-catenin by GSK3 induced its rapid proteasome mediated degradation.\(^4^9\) Following Wnt binding to a receptor complex composed of members of the Frizzled family the Axin/APC/GSK3 is inhibited leading to a block in $\beta$-catenin phosphorylation by GSK3. Hypophosphorylated $\beta$-catenin accumulates in the cytoplasm and is translocated to the nucleus where it regulates target gene expression.\(^4^9\) Deregulation of the Wnt signaling pathway is a hallmark of several types of leukemias. \(^5^0\) Different molecular mechanisms
have been implicated in the abnormal activation of the Wnt pathway including the functional loss of Wnt antagonists resulting in leukemogenesis through deregulation of cell proliferation and differentiation. Although it is now clear that the Wnt signaling pathway is now recognized as one of the major player in the genesis of leukemia, the question whether this pathway can be targeted by drugs remains an object of study.

The niche is anatomically and functionally defined and has an endosteal and perivascular compartment within the bone marrow. Within the niche, there are critical bidirectional signals that ensure the regulation of normal HSC numbers and maintenance of the quiescent long term HSC pool. Cells that are of mesenchymal origin, the adventitial reticular cells, have been shown to alter stem cell function. These cells express high levels of the CX chemokine ligand12 (CXCL12 also called stromal-derived factor 1, SDF1) and are located between vessels and bone. Targeted deletion of CXCR4 (the ligand for CXCL12) led to a severe reduction in HSC numbers and increased chemosensitivity. The interactions between CXCR4 and SDF1 are important in the localization and retention of HSC and progenitor cells within the niche and they play a critical role in colonization of the bone marrow by HSCs during early development as demonstrated by the evidence that SDF1 deficient embryos have severely reduced HSC numbers and function.

The interaction between CXCR4 and CXCL12 appears to be critical for leukemic cell maintenance. The leukemic cells seem to have the unique capacity to directly modulate the niche at the expense of normal hematopoietic stem and progenitor cells by down-regulating CXCL12 levels in the areas of leukemia infiltration. Stem cell factor, secreted by the leukemic cells, represents a further niche regulator leading to abnormal engraftment of normal HSC in the tumor-infiltrated microenvironment. There are emerging evidences that the complex interactions between LSCs and their niche may be targeted to selectively deplete the repopulating ability of LSCs and to favor the normal HSC counterparts. In order to obtain a selective eradication of LSCs the niche targeted therapy requires a high degree of selectivity towards the aberrant interaction between the leukemic clone and the microenvironment. These could include self renewal pathways such as Notch or...
Wnt, homing mechanisms, or cell adhesion molecules. There are data supporting the role of the Notch pathway in the maintenance of leukemic stem cells and Wnt signaling in blast crisis CML stem cells.\textsuperscript{56} Importantly, there are evidences that both these pathways are, at least partially, regulated by the niche. Adhesion molecules represent attractive candidate targets for LSC specific therapies. Direct targeting of CXCR4 with chemical compounds may represent another developing strategy.\textsuperscript{57} The CXCR4 antagonist AMD3465 has been shown to overcome the protective effects of stromal cells towards chemotherapeutical agents. Further studies have also shown that AMD3100 treatment, another CXCR4 antagonist currently used mainly to mobilize normal HSC, results in leukemic cells mobilization and increased chemosensitivity.\textsuperscript{58} Furthermore, targeting CXCR4 appears to have beneficial effects against leukemic clone.

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**Figure legends**

**Figure 1**: Schematic representation of the molecular pathway activated by BCR-ABL.

Bcr-Abl phosphorylation of BCR Tyr177 is essential for BCR-ABL mediated leukemogenesis. The BCR-ABL Grb2 complex recruits Sos, (Son of Sevenless), which is constitutively associated with the Grb2 SH3 domain. BCR-ABL-Grb2-Sos complex stimulates conversion of the inactive GDP-bound form of Ras to its active GTP-bound state and the activation of the scaffold adapter GRB2-associated binding protein 2 (GAB2). As a consequence, GRB2/GAB2/SOS complex causes constitutive activation of RAS downstream pathway so activating MEK1/2 and MAPK proteins causing, as a final result, an abnormal cell proliferation. In addition this complex activates the phosphatidylinositol 3-kinase (PI3K)/AKT pathway represented in detail in figure 2 panel B.

**Figure 2**: BCR-ABL related pathways: Panel A: Schematic representation of RAS/PI3K signaling pathway and AKT pathway downstream of BCR-ABL. (PI3K)/AKT pathway promotes survival by suppressing the activity of forkhead O (FOXO) transcription factor, enhance cell proliferation by inducing p27 proteosomal degradation and by mTOR activation. PI3K activates Akt kinase which represents a key downstream effector by exerting many cellular effects through the phosphorylation of downstream substrates including Bad, caspase 9, Mdm2 and Ask1 that regulate the apoptotic machinery, therefore resulting into prolonged survival and expansion of the abnormal clone. The mammalian target of rapamycin (mTOR) lies downstream of Akt in the PI3K kinase pathway. It is a
serine/threonine kinase made of two complexes, mTORC1 controlling transit from G1 phase to S phase of the cell cycle and mTORC2 which phosphorylates Akt leading to its full activation.

Panel B: Schematic representation of the Hedgehog pathway. Hedgehog pathway activation is initiated when Hh ligand binds to Patched (PTCH) which moves away from a second transmembrane protein called Smoothened (Smo). Smo signals to a cytoplasmatic complex that releases a transcription factor (Gli) which translocates to the nucleus where it activates the Hh target genes.

Panel C: schematic representation of Wnt pathway.

The major effector of the Wnt pathway is β-catenin. In the absence of Wnt signaling β-catenin is retained in the cytoplasm through a direct interaction with Axin, APC and GSK3. β-catenin phosphorylation by GSK3 induces its rapid proteasome mediated degradation. Bcr-Abl, by binding ubiquitinated β−catenin stabilizes it from ubiquitination thus increasing the β-catenin levels. Following Wnt binding to a receptor complex composed of members of the Frizzled family the Axin/APC/GSK3 is inhibited leading to a block in β-catenin phosphorylation by GSK3. Hypophosphorylated β-catenin accumulates in the cytoplasm and is translocated to the nucleus where it regulates target gene expression.
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