Differential Expression and Clinical Significance of Tyrosine-phosphorylated STAT3 in ALK+ and ALK− Anaplastic Large Cell Lymphoma

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ABSTRACT

Purpose: Recent data suggest that nucleophosmin-anaplastic lymphoma kinase (NPM-ALK) activates signal transducers and activators of transcription 3 (STAT3) directly, and ALK expression correlates with STAT3 activation in non-Hodgkin’s lymphomas. In this study, we evaluated comprehensively STAT3 activation status in anaplastic large cell lymphoma (ALCL) cell lines and pretreatment ALCL tumors.

Experimental Design: The study included five ALK+ ALCL cell lines and 80 systemic ALCL tumors (31 ALK+, 49 ALK−) that were formalin fixed and paraffin embedded. All 80 patients with systemic ALCL were treated with doxorubicin-based chemotherapy. The STAT3 activation status in cell lines was determined using Western blots and an antibody that reacts specifically with the phosphorylated tyrosine 705 (pSTAT3 tyr705). In systemic ALCL tumors, STAT3 was considered active when ≥20% of neoplastic cells show unequivocal nuclear immunostaining for pSTAT3 tyr705.

Results: All five ALK+ ALCL cell lines showed strong pSTAT3 tyr705 expression on Western blots. In systemic ALCL, STAT3 activation was detected in 49 of 80 (61%) ALCL tumors: 26 of 31 (84%) ALK+ tumors and 23 of 49 (47%) ALK− tumors. ALK expression correlated significantly with STAT3 activation (P < 0.0001). Clinical follow-up data were available for 72 patients. In the ALK+ group, the lack of STAT3 activation correlated with a favorable 5-year overall survival (P = 0.0076) but not failure-free survival. In the ALK+ group, patients with inactive STAT3 showed a trend toward longer overall survival (P = 0.09) and failure-free survival (P = 0.19). Importantly, all five ALK+ ALCL patients with inactive STAT3 survived without treatment failure after a median follow-up of 83 months.

Conclusions: STAT3 activation correlates with but is not strictly dependent on ALK expression in ALCL. Lack of STAT3 activation appears to correlate with a favorable clinical outcome in ALCL.

INTRODUCTION

ALCL, as defined in the recently published WHO classification, is a distinct type of non-Hodgkin lymphoma of T/null cell immunophenotype with anaplastic cytological features and expression of CD30 (1). A subset of ALCL tumors carries nonrandom chromosomal translocations involving the ALK gene on chromosome 2, leading to overexpression of ALK protein (2, 3). The t(2;5) is the most common translocation in ALCL, and it leads to the formation of a chimeric protein NPM-ALK (3). A number of other translocations leading to fusion of the ALK gene with other partner genes also have been described previously (4–7). Thus far, the fusion gene products of all translocations resulting in ALCL tumors are more prevalent in young patients and are associated with a favorable outcome (9–11). Although there is evidence that ALK expression is also biologically important in ALCL, the exact role of ALK in these tumors is incompletely understood. Recently, evidence has been accumulating that NPM-ALK may promote cell survival and tumorogenesis by constitutively activating a number of cell signaling pathways, including the STAT pathway (12–14).

STAT proteins constitute a family of seven, highly conserved, latent transcription factors that play a role in signal transduction in response to cytokine stimulation (15). Upon stimulation, STAT proteins are phosphorylated by the Janus kinases at the tyrosine 705 residue, dimerize, and migrate to the nucleus where they function as transcription factors modulating the expression of a host of genes involved in cell proliferation and apoptosis (16). STAT3 has been shown to be an oncogene.

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2The abbreviations used are: ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; NPM, nucleophosmin; STAT, signal transducers and activators of transcription; TUNEL, terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling; FFS, failure-free survival; OS, overall survival; IL, interleukin.
(15), and its constitutive activation has been found in a variety of human neoplasms, including some types of non-Hodgkin lymphoma such as ALCL (14, 17, 18). It has been recently shown that NPM-ALK is capable of directly phosphorylating and activating STAT3 molecules in vitro (14). In the same study, the authors also examined STAT3 activation status in a variety of non-Hodgkin lymphomas by detecting nuclear localization of STAT3 using immunohistochemistry and an antibody reactive with STAT3; they found that STAT3 activation is closely linked to ALK expression in non-Hodgkin’s lymphomas (14).

In light of these previous findings related to ALK expression and STAT3 activation in ALCL, we assessed STAT3 activation status in ALCL using five ALK+ ALCL cell lines and a large series of pretreatment ALCL tumors. In contrast with the study conducted by Zamo et al. (14), we evaluated STAT3 activation using an antibody that reacts specifically with the phosphorylated tyrosine 705 residue of the STAT3 protein based on our preliminary finding that immunostaining of pSTAT3( Tyr705) is much easier to interpret than STAT3. We also based on our preliminary finding that immunostaining of phosphorylated tyrosine 705 residue of the STAT3 protein

**MATERIALS AND METHODS**

**ALCL Cell Lines.** The five ALK+ ALCL cell lines included Karpas 299 [a gift from Dr. Marshall Kadin (Boston, MA)], SR-786, SU-DHL-1 (both from DSMZ, Braunschweig, Germany), JB-6, and TS-G1 [gifts from Dr. Dan Jones (Houston, TX)]. All cell lines have been previously shown to carry the t(2;5) and express ALK protein. All ALCL cell lines were kept in a medium that contained RPMI 1640 (Life Technologies, Inc., Gaithersburg, MD) supplemented with 10% heat-inactivated fetal bovine serum, HEPES buffer, 50 μg/ml streptomycin, 2 mM glutamine, and 50 μg/ml penicillin and kept in a humidified incubator at 37°C with 5% CO2. For preparation of cell blocks, cell lines were grown to mid-logarithmic phase, fixed overnight in buffered formalin, and embedded in paraffin.

**Protein Extraction and Western Blot Analysis.** Western blot analysis was performed using standard techniques. Briefly, the cells were washed in PBS (pH 7.5) and lysed in a buffer containing 50 mM Tris-HCl (pH 8.0), 150 mM NaCl, 0.1% SDS, 1% NP40, 1 mM phenylmethylsulfonyl fluoride, 5 μg/ml aprotinin, 1 mM sodium vanadate, and 5 μg/ml leupeptin. After incubation on ice for 15 min, the lysates were subjected to centrifugation at 12,000 rpm, and the supernatants were collected. Protein concentration was determined with a protein assay kit (Bio-Rad, Hercules, CA). Each lane of a 5–12% polyacrylamide slab gel received 80 μg of protein. After electrophoresis and transfer to a nitrocellulose membrane (Bio-Rad) by electroblotting, blots were probed with specific primary and secondary antibodies and the enhanced chemiluminescence detection system (Amershams, Arlington Heights, IL), according to the manufacturer’s protocol. The antibodies were used at dilutions of 1:1000.

**Patient Group.** The study group included 61 patients with systemic ALCL seen at The University of Texas M. D. Anderson Cancer Center between 1984 and 2002 and 19 patients with systemic ALCL seen at the University of Freiburg between 1982 and 2002. The study was carried out in accordance with an Institutional Review Board-approved protocol. Overall, there were 50 males and 30 females with a median age of 41 years (range, 4–82 years). All patients were treated with a doxorubicin-based chemotherapeutic regimen. Detailed clinical and follow-up data were available in 72 cases, and the follow-up period ranged from 1 to 129 months (median, 46 months).

**ALCL Tumors and Tissue Microarray Construction.** Tumors fulfilled the diagnostic criteria of ALCL as defined in the WHO classification (1). All ALCL tumors were CD30+ and either a T-cell (65 cases) or null-cell (15 cases) immunophenotype. Thirty-one (39%) tumors were ALK+ and 49 (61%) were ALK−. All ALCL tumor biopsy specimens were obtained before therapy and were fixed in formalin, routinely processed, and embedded in paraffin. Fifty ALCL tumors were included in two tissue microarrays, and 30 tumors were assessed using full-tissue sections. To construct the ALCL tissue microarrays, three representative cores from each tumor were selected from the paraffin tissue blocks. Triplicate cores from two reactive lymph nodes were included in the tissue microarrays as internal controls. Seven cases of primary cutaneous ALCL tumors were also included for comparison. The tissue microarrays were constructed using a manual tissue arrayer (Beecher Instruments, Silver Spring, MD).

**Antibodies and Immunohistochemistry.** Monoclonal antibodies reactive with pSTAT3( Tyr705) and STAT3 were obtained from Santa Cruz Biotechnology (1:25; Santa Cruz, CA). Ki-67 was purchased from Immunotech (1:120; Westbrook, ME). Heat-induced epitope retrieval was performed for all immunostains. 3,3’-Diaminobenzidine/H2O2 (Biogenex, San Ramon, CA) was used as a chromogen with hematoxylin as the counterstain. For all immunostains performed using tissue microarray sections, the percentage of positively stained cells was determined by counting at least 200 neoplastic cells in each of the triplicate cores. The final percentage of positively stained cells was the highest percentage obtained on the individual tissue cores. Using full tissue sections, at least 1,000 cells were counted in areas of greatest staining. Immunostaining for pSTAT3( Tyr705) was performed in duplicate, and the final percentages were averaged. ALCL tumors were considered to be STAT3 active when ≥20% of neoplastic cells showed unequivocal, nuclear pSTAT3( Tyr705) immunostaining, regardless of the staining intensity. This cutoff level is close to that used in the previous study by Zamo et al. (14) and was chosen in this study based on a distribution histogram (data not shown). For immunostaining with STAT3, cases were assessed for both the presence as well as distribution of immunostaining (cytoplasmic and/or nuclear). Using STAT3 immunostaining, ALCL tumors were considered to be STAT3-active when ≥20% of neoplastic cells showed unequivocal nuclear localization of the stain. The percentage of Ki-67-positive cells was designated as the proliferation rate. All immunostained slides were evaluated without knowledge of the ALK expression status or clinical outcome.

**TUNEL Assay.** The TUNEL assay used in this study has been described previously (19). Briefly, deparaffinized tissue sections were pretreated with proteinase K for 25 min at 37°C and then incubated for 5 min in 3% H2O2 in PBS at pH 7.4 to block endogenous peroxidase activity. Terminal deoxynucleotidyl
transferrin was used as a negative control for immunochemistry. Tissue sections of K562 cells were incubated with DNase I (2.5 μg in 50 μl/slide in Tris-buffered saline containing 6 mm MgCl2) for 30 min at 37°C. Tissue sections of K562 cells incubated with a reaction mixture lacking terminal deoxynucleotidyl transferase served as negative controls. The percentage of positively staining cells counted on each of the satisfactorily stained cores was determined. The final percentage was the highest value obtained and was designated as the apoptotic rate.

Statistical Analysis. The association between STAT3 activation and various parameters was evaluated by Fisher’s exact test. Correlation of proliferation and apoptotic rates, analyzed as continuous variables, with STAT3 activation was based on the Mann-Whitney U test. Survival analysis was performed separately in ALK+ ALCL and ALK− ALCL groups. FFS was measured from the beginning of treatment to the time of primary treatment failure, relapse, or last follow-up. OS was measured from the beginning of treatment to the time of last follow-up or death from any cause. Actuarial survival was measured by the Kaplan-Meier method. The statistical independence between possible prognostic variables was evaluated by multivariate analysis using Cox’s proportional hazards model. All statistical calculations were performed using the Statview software (Abacus Concepts, Inc., Berkeley, CA).

RESULTS

Expression of pSTAT3 tyr705 in ALCL Cell Lines. As shown in Fig. 1, Western blot studies revealed that all five ALK+ ALCL cell lines expressed pSTAT3 tyr705, which was at roughly M_r ~92,000. The staining intensity was variable among these cell lines, with Karpas 299 expressing the highest level of pSTAT3 tyr705. Immunohistochemical staining for pSTAT3 tyr705 was performed on cell blocks prepared from three of these five ALK+ ALCL cell lines (Karpas 299, SU-DHL-1, and SR786), and all three cell lines showed immunoreactivity for pSTAT3 tyr705 that was confined to the nucleus (data not shown). Similar experiments were performed using two cell lines included as negative controls, LNCaP (prostate cancer cells) and U927 (myelomonocytic leukemia cells), both of which were negative for pSTAT3 tyr705 on Western blots and by immunohistochemistry.

pSTAT3 tyr705 Expression in ALCL Tumors. Immunohistochemical staining for pSTAT3 tyr705 was then performed on 80 systemic ALCL tumors included in this study (illustrated in Fig. 2). Overall, pSTAT3 tyr705 was positive in 49 of 80 (61%) ALCL tumors. Twenty-six of 31 (84%) ALK+ ALCL tumors and 23 of 49 (47%) ALK− ALCL tumors showed nuclear positivity for pSTAT3 tyr705. Immunostaining of pSTAT3 tyr705 confined to the cytoplasm was observed only in rare cases, and they were considered pSTAT3-inactive for the purpose of this study. Using a cutoff of ≥20% neoplastic cells showing nuclear immunostaining for pSTAT3 tyr705, we found a significant correlation between STAT3 activation and ALK expression (P < 0.0001, Fisher’s exact test). In comparison, benign reactive lymph nodes as well as all 7 cases of cutaneous ALCL were negative for pSTAT3 tyr705.

To compare our findings with the results of a previous study by Zamo et al. (14), who used anti-STAT3 to detect STAT3 activation, we performed STAT3 immunohistochemistry using an ALCL tissue microarray that contained 34 tumors (8 ALK+ and 26 ALK−). Of these 34 tumors, 33 (97%) showed positive staining for the STAT3 protein. As sum-

Association of pSTAT3 tyr705 Expression with Presenting Clinical and Laboratory Findings of ALCL Patients. The presenting clinical and laboratory findings of the 80 ALCL patients are summarized in Table 2. pSTAT3 tyr705 positivity did not correlate with any of the clinical parameters assessed, with the exception of a positive correlation with young patient age (P = 0.02, Mann-Whitney U test). This might be attributed to the correlation with ALK positivity because patients with such tumors were generally younger. No correlation between pSTAT3 tyr705 and tumor proliferation or apoptotic rates, assessed as continuous variables, was identified.

Survival Analysis. For 72 ALCL patients with follow-up data, the 5-year OS was 68% for patients with STAT3-active tumors compared with 94% for patients with STAT3-inactive tumors (P = 0.0076, log-rank; Fig. 4A). There was no signifi-

Fig. 1 Western blot analysis of five ALK+ ALCL cell lines, showing pSTAT3 tyr705 expression in all five cell lines.
cantly statistical difference in FFS between these two groups \( (P = 0.55, \log\text{-rank}) \). We then correlated STAT3 activation status with clinical outcome in the ALK\(^+\) ALCL and ALK\(^-\) ALCL groups separately. In the ALK\(^-\) ALCL group, lack of STAT3 activation correlated significantly with longer 5-year OS: 70% for patients with STAT3-active tumors compared with 92% for patients with STAT3-inactive tumors \( (P = 0.03, \log\text{-rank, Fig. 4B}) \). By contrast, the 5-year FFS was not significantly different between these two groups: 67% for patients with STAT3-active tumors compared with 69% for patients with STAT3-inactive

\[\text{Fig. 2} \quad \text{Immunohistochemical staining with pSTAT3 tyr705 in ALK}\(^+\) (left panels) and ALK\(^-\) (right panels) ALCL tumors. Note the relatively lower intensity of pSTAT3 tyr705 immunostaining in ALK\(^-\) ALCL compared with ALK\(^+\) ALCL tumors.}\]

\[\text{Fig. 3} \quad \text{Immunohistochemical staining with STAT3 in ALK}\(^+\) (left panels) and ALK\(^-\) (right panels) ALCL tumors. All tumors that immunostained with anti-STAT3 showed cytoplasmic staining, which in some cases also demonstrated nuclear localization of the staining.}\]
tumors ($P = 0.67$, log-rank). In the ALK$^+$ ALCL group, all 5 patients with STAT3-inactive tumors survived without treatment failure in the follow-up time period (median, 83 months), and lack of STAT3 activation showed a trend toward longer OS ($P = 0.09$) and FFS ($P = 0.19$; log-rank, Fig. 4, C and D).

**DISCUSSION**

In this study, we assessed the STAT3 activation status in ALK$^+$ ALCL cell lines and pretreatment ALCL tumors using a monoclonal antibody that recognizes the tyrosine-phosphorylated form of STAT3, pSTAT3$^{tyr705}$. The concept that this antibody recognizes only the activated form of STAT3 is supported by several lines of evidence. First, it has been shown previously that pSTAT3$^{tyr705}$ immunoreactivity correlates with levels of STAT3 DNA binding activity, as measured by electrophoretic mobility shift assay (20). Second, in one of our recent studies, we found that pSTAT3$^{tyr705}$ immunoactivity on Western blots increases after interleukin stimulation (21). Third, as shown in this study, pSTAT3$^{tyr705}$ immunoactivity on tissue sections is confined to the nucleus in the vast majority of cases. Thus, this antibody is a useful tool to assess the activation status of STAT3. The usefulness of the pSTAT3$^{tyr705}$ antibody is further illustrated by the observation that its immunoreactivity on Western blots correlates with that on tissue sections of ALCL cell lines.

pSTAT3$^{tyr705}$ was detected in all five ALK$^+$ ALCL cell lines using Western blotting, and STAT3 activation correlated significantly with ALK expression in ALCL cell lines and tumors using immunohistochemistry. Namely, using immunohistochemistry, all five ALK$^+$ ALCL cell lines examined were positive for pSTAT3$^{tyr705}$, and the correlation between ALK expression and STAT3 activation in our study group was highly significant ($P < 0.0001$). This finding supports the concept that NPM-ALK activates STAT3, as suggested in a recent study (14). NPM-ALK is believed to be important in the pathogenesis of ALK$^+$ ALCL. Although the mechanism underlying the tumorigenicity of NPM-ALK in ALCL is incompletely understood, it is likely that the chimeric protein deregulates cell cycle progression and apoptosis control by constitutively activating a number of mediators involved in several cell signaling pathways (2). Because NPM-ALK constitutively activates multiple signaling pathways, it is of interest to determine the relative importance of these pathways. STAT3 has been shown to have oncogenic potential (22), and its aberrant constitutive activation has been identified in a variety of human neoplasms (14, 17, 18), including ALCL (14). Therefore, it seems likely that STAT3 serves as a mediator of the oncogenic effect of NPM-ALK in ALK$^+$ ALCL leading to promotion of cell growth. Nevertheless, we did not detect a significant correlation between STAT3 activation and proliferation or apoptotic rates in ALCL tumors. This might be because ALCL tumors lacking STAT3 activation harbor other mechanisms that are as effective as constitutive STAT3 activation in deregulating proliferation and apoptosis.

A minority (5 of 31, 16%) of ALK$^+$ ALCL tumors lacked evidence of STAT3 activation in our study. As mentioned above, all such tumors showed immunostaining with STAT3 that was confined to the cytoplasm. In the study by Zamo et al. (14), 1 of 21 (5%) ALK$^+$ ALCL tumors also failed to show evidence of STAT3 activation and lacked nuclear localization of STAT3 immunostaining. The explanation for the lack of STAT3 activation despite the presence of ALK overexpression is unclear. One possibility is that activation of STAT3 requires the specific combination of NPM and ALK, and ALK fusion gene products that include a fusion gene partner other than NPM are suboptimal in activating STAT3, although the ALK portion includes the tyrosine kinase domain. Generally, ALCL tumors that carry the t(2;5) exhibit both cytoplasmic and nuclear staining for the ALK protein, whereas in ALCL tumors with other translocations, immunostaining with ALK is confined to the cytoplasm (23). Among the five ALK$^+$ ALCL tumors that were STAT3 inactive, four cases clearly showed only cytoplasmic staining for ALK (data not shown). Accurate assessment of the ALK immunostaining pattern in the fifth case was limited by extensive tumor necrosis. These findings suggest that STAT3-inactive, ALK-positive ALCL tumors do not carry the t(2;5) and, thereby, do not harbor the NPM-ALK chimeric protein. Because activation of STAT3 seems to require physical binding of STAT3 with ALK, it is perceivable that the fusion gene partners of ALK can influence the efficiency of binding between ALK and STAT3. An alternative explanation is that persistent aberrant STAT3 activation in ALK$^+$ ALCL requires simultane-
ous defects in the system that are normally responsible for turning off activated STAT3. In support of this hypothesis, Zhang et al. (24) demonstrated that ALK+ ALCL lack protein inhibitor of activated STAT3 and/or protein phosphatase 2A, both of which may inhibit STAT3 activation.

One interesting observation in this study is that roughly half (23 of 49, 47%) of ALK+ ALCL tumors showed pSTAT3 tyr705 positivity. This finding indicates that STAT3 activation is not strictly dependent on ALK expression in ALCL and contradicts the conclusion drawn previously by others (14). We believe that the lack of dependency on ALK for STAT3 activation in ALCL is not entirely surprising because many other types of human neoplasms that are ALK negative have constitutively activated STAT3. Moreover, multiple mechanisms of activating STAT3 have been identified (16, 25–27). In this study, ALK+ ALCL tumors had a generally stronger pSTAT3 tyr705-staining intensity compared with ALK− ALCL, in keeping with the concept that the mechanism(s) of STAT3 activation in ALK− ALCL is different from that in ALK+ ALCL. It is possible that in ALK− ALCL, STAT3 is activated by cytokines. Such a putative mechanism would be analogous to that seen in plasma cell myeloma in which tumor cells are stimulated by IL-6 (28), Hodgkin lymphomas that are stimulated by IL-13 (27, 29), and T-cell lymphomas that are stimulated by IL-2 (17). In addition to mediation by extracellular stimuli, STAT3 activation also has been shown to be mediated by intracellular oncoproteins such as SRC (30). ALK+ ALCL tumors have been shown also to have defects in the pathway responsible for turning off activated STAT3 (24). Therefore, in an analogous fashion constitutive STAT3 activation in ALK− ALCL tumors might be secondary to defects in degradation rather than overproduction of activated STAT3.

Because immunohistochemical evaluation of STAT3 activation in ALCL was previously assessed using an antibody reactive for STAT3 (pan-STAT3; Ref. 14), we performed immunohistochemistry using this antibody for comparison. Our results suggest that assessment based on STAT3 immunostain is less sensitive than pSTAT3 tyr705 immunostaining, particularly in cases with a relatively low-level of STAT3 activation. This is because cytoplasmic staining of STAT3, which highlights the inactivated STAT3 molecules, is usually so intense that the presence of relatively weak nuclear staining cannot be discerned with accuracy. By contrast, because anti-pSTAT3 tyr705 detects only the activated STAT3 molecules localized to the nucleus, there is no interference by cytoplasmic staining using this immunostain. We believe that such a difference in sensitivity between the two antibodies may explain the discrepancy be-

Fig. 4 A, OS for the entire study group. B, OS for the ALK− ALCL group. C, OS for the ALK+ ALCL group. D, FFS for the ALK− ALCL group.
between the frequencies of STAT3 activation in our ALK-ALCL tumors and those of others (14).

Our results suggest that the activation status of STAT3 may have prognostic significance in patients with ALCL. In our group of ALCL patients, those whose tumors showed evidence of STAT3 activation show a trend for a less favorable clinical outcome in comparison to patients whose tumors lacked STAT3 activation. Similar findings have been observed in a number of different neoplasms. For example, detection of high levels of pSTAT3 Tyr705 staining in renal cell carcinomas has been found to be an independent prognostic factor associated with a poor clinical outcome (31). Likewise, detection of STAT3 activation is associated with an adverse clinical outcome in patients with prostatic carcinoma (20), squamous cell carcinoma of the head and neck region (32), and acute myeloid leukemia (33). Although ALK expression has been established as an independent prognostic factor in patients with ALCL (8, 10, 11), a number of studies have indicated the presence of a subset of patients with ALK+ALCL that follow an adverse clinical course (9, 34). Although our numbers are relatively small, we believe that the lack of relapse in all 5 patients with ALK+/pSTAT3 Tyr705− ALCL tumors with long-term follow-up (median, 83 months) is interesting and important. Likewise, in the ALK−ALCL group, lack of STAT3 activation also showed a more favorable outcome. Overall, our findings suggest that the STAT3 activation status may be a useful prognostic marker in ALCL regardless of ALK status. However, such a conclusion needs to be validated in a larger cohort of patients, particularly in the ALK+ group. Moreover, with the progress in development of specific therapies targeting activated STAT3 (35), detection of pSTAT3 Tyr705 may play a role in identifying patients who may respond to such a treatment option.

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