Long-term anticoagulation treatment for acute venous thromboembolism in patients with and without cancer

The SWIss Venous ThromboEmbolism Registry (SWIVTER) II

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Summary

In patients with acute cancer-associated thrombosis, current consensus guidelines recommend anticoagulation therapy for an indefinite duration or until the cancer is resolved. Among 1,247 patients with acute venous thromboembolism (VTE) enrolled in the prospective Swiss Venous Thromboembolism Registry (SWIVTER) II from 18 hospitals, 315 (25%) had cancer of whom 179 (57%) had metastatic disease, 159 (50%) ongoing or recent chemotherapy, 83 (26%) prior cancer surgery, and 63 (20%) recurrent VTE. Long-term anticoagulation treatment for >12 months was more often planned in patients with versus without cancer (47% vs. 19%; p<0.001), with recurrent cancer-associated versus first cancer-associated VTE (70% vs. 41%; p<0.001), and with metastatic versus non-metastatic cancer (59% vs. 31%; p<0.001). In patients with cancer, recurrent VTE (OR 3.46; 95%CI 1.83–6.53), metastatic disease (OR 3.04; 95%CI 1.86–4.97), and the absence of an acute infection (OR 3.55; 95%CI 1.65–7.65) were independently associated with the intention to maintain anticoagulation for >12 months. In conclusion, long-term anticoagulation treatment for more than 12 months was planned in less than half of the cancer patients with acute VTE. The low rates of long-term anticoagulation in cancer patients with a first episode of VTE and in patients with non-metastatic cancer require particular attention.

Keywords

Anticoagulation, cancer, venous thromboembolism

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Financial support:
This study was funded by Sanofi-Aventis (Suisse) SA, Meyrin, Switzerland.

Received: January 2, 2011
Accepted after minor revision: February 4, 2011
Prepublished online: April 7, 2011

doi:10.1160/TH11-01-0002
Thromb Haemost 2011; 105: 962–967

Introduction

In patients with active cancer, the incidence of venous thromboembolism (VTE) has substantially increased during the past decade (1). VTE represents the second leading cause of death in cancer patients, and it is a significant predictor of mortality in hospitalised patients with cancer (2–5). Approximately one third of patients treated for cancer-associated VTE and 5% of those treated for acute VTE without cancer die within three months after VTE diagnosis (6, 7). Development of VTE within two years after diagnosis of cancer is an independent predictor of mortality regardless of disease stage or the number of co-morbidities (8). In comparison to patients without cancer, the risk of recurrent VTE in patients with cancer is increased both on anticoagulation therapy (9, 10) and after discontinuation of anticoagulation therapy (11, 12).

In patients with cancer-associated VTE, current consensus guidelines of the American College of Chest Physicians (13) and the American Society of Clinical Oncology (14) recommend anticoagulation therapy for an indefinite duration or until the cancer is resolved. A systematic review of the randomised controlled trials demonstrated that low-molecular-weight heparin (LMWH) halves the risk of VTE recurrence as compared to vitamin K-antagonists (VKA) in cancer patients with acute VTE (6). Thus, the recommended modalities for treating patients with cancer-associated thrombosis include LMWH for 3–6 months (grade 1A), followed by VKA or continued LMWH indefinitely or until the cancer is resolved (grade 1C). We aimed to explore the use of long-term anticoagulation and its clinical predictors in patients with acute VTE according to the presence of cancer.

Methods

Patients

Between January 2009 and May 2010, four academic and fourteen non-academic acute care hospitals in Switzerland enrolled 1,247 consecutive patients with acute deep-vein thrombosis (DVT) or pulmonary embolism (PE) in the prospective SWIss Venous Throm-

boEmbolism Registry (SWIVTER) II. Inclusion criteria were age ≥18 years and objectively confirmed acute VTE event, and there were no exclusion criteria. Eligible patients were enrolled during clinical inpatient or outpatient visits. DVT had to be objectively confirmed by compression ultrasound or phlebography, and PE by contrast-enhanced chest computed tomography, ventilation perfusion scan, or conventional pulmonary angiography. SWIVTER did not issue recommendations on the diagnostic work-up of cancer. The study was approved by the local ethics committees of the participating hospitals.

Data and statistical analysis

A standardised electronic case report form (CRF) was used for collecting anonymous data on patient age, sex and hospital status (in- or outpatient) at the time of VTE diagnosis, localisation of VTE, risk factors for VTE and bleeding, planned duration and modalities of anticoagulation treatment, and clinical follow-up information, such as mortality, recurrent VTE, and bleeding requiring medical attention at 30 days after VTE diagnosis. For the planned duration of anticoagulation, physicians were asked to categorise patients into one of the following groups: ≤3 months, >3–6 months, >6–12 months, or long-term (>12 months). Data were captured into the CRF directly by physicians in charge of the patient's care or by dedicated study physicians or nurses. The planned duration of anticoagulation treatment was obtained from the hospital discharge report if data were not entered directly by the physician in charge.

Patients were separated into two groups according to the presence of cancer. No uniform identification procedure was used to define cancer and to identify cancer patients. Therefore, data on the planned duration of anticoagulation treatment are also presented for various

Table 1: Demographics, chronic and acute comorbidities according to presence of cancer.

	Total N = 1,247	Cancer N = 315	Non-cancer N = 932	P-value
Demographics				
Age, mean years ± SD	61 ± 18	66 ± 14	60 ± 19	<0.001
Women, n (%)	605 (48.5)	138 (43.8)	467 (50.1)	0.053
Inpatient at the time of diagnosis, n (%)	478 (38.3)	145 (46.0)	333 (35.7)	0.001
Hospital days, median (IQR)	11 (7–20)	14 (8–22)	10 (6–19)	0.002
Chronic comorbidities				
Prior VTE, n (%)	288 (23.1)	63 (20.0)	225 (24.1)	0.13
Obesity, n (%)	174 (14.0)	25 (7.9)	149 (16.0)	<0.001
Varicosis, n (%)	164 (13.2)	29 (9.2)	135 (14.5)	0.017
Chronic lung disease, n (%)	140 (11.2)	54 (17.1)	86 (9.2)	<0.001
Renal failure, n (%)	89 (7.1)	23 (7.3)	66 (7.1)	0.90
Oral contraceptives, n (%)	82 (6.6)	2 (0.6)	80 (8.6)	<0.001
Congestive heart failure, n (%)	81 (6.5)	11 (3.5)	70 (7.5)	0.012
History of stroke/TIA, n (%)	67 (5.4)	16 (5.1)	51 (5.5)	0.79
Known thrombophilia, n (%)	36 (2.9)	4 (1.3)	32 (3.4)	0.047
Acute comorbidities within 30 days				
Prior hospitalisation, n (%)	332 (26.6)	147 (46.7)	185 (19.9)	<0.001
Bed rest >3 days, n (%)	231 (18.5)	80 (25.4)	151 (16.2)	<0.001
Surgery, n (%)	170 (13.6)	56 (17.8)	114 (12.2)	0.013
Acute infection/sepsis n (%)	148 (11.9)	47 (14.9)	101 (10.8)	0.053
Trauma/fracture n (%)	91 (7.3)	11 (3.5)	80 (8.6)	0.003
Inflammatory/rheumatic disease, n (%)	89 (7.1)	15 (4.8)	74 (7.9)	0.058
Acute respiratory failure, n (%)	83 (6.7)	29 (9.2)	54 (5.8)	0.036
ICU admission, n (%)	69 (5.5)	22 (7.0)	47 (5.0)	0.19
Bleeding requiring attention, n (%)	60 (4.8)	19 (6.0)	41 (4.4)	0.24
Acute heart failure, n (%)	37 (3.0)	8 (2.5)	29 (3.1)	0.61
Thrombocytopenia, n (%)	33 (2.7)	20 (6.4)	13 (1.4)	<0.001
Ischaemic stroke or palsy, n (%)	27 (2.2)	11 (3.5)	16 (1.7)	0.06

VTE, venous thromboembolism; TIA, transient ischaemic attack; ICU, intensive care unit.

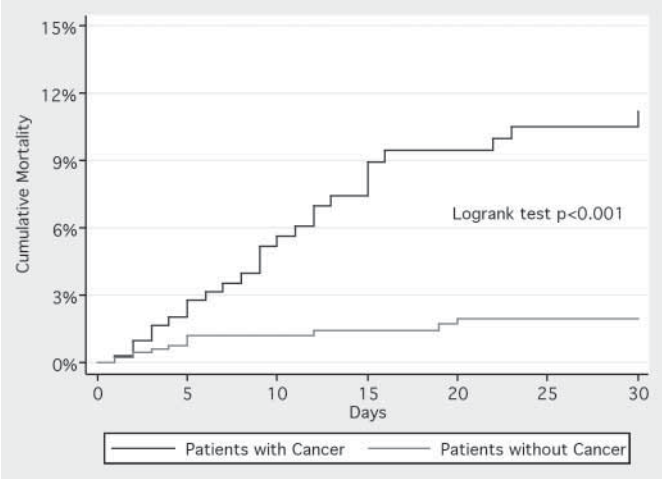

Figure 1: Kaplan-Meier cumulative 30-day mortality in patients with and without cancer.

subgroups of patients with cancer: recurrent and first VTE, metastatic and non-metastatic disease, ongoing or recent chemotherapy within six months, recent surgery within six months, and treatment in academic and non-academic hospitals. Continuous variables with a normal distribution were described as means with standard deviations (SD), and group comparisons were performed with the t-test; continuous variables with skewed distribution were presented as median values with interquartile ranges (IQR), and group comparisons were performed with a rank-sum test. Discrete variables were presented as frequencies and percentages, and group comparisons were performed using the chi square or Fisher's exact test. Bonferroni's correction for multiple group comparisons indicated a p-value of less than 0.001 for statistical significance.

Univariate logistic regression analysis reporting odds ratios (OR) with 95% confidence intervals (CI) was conducted to identify clinical predictors for the use of indefinite-duration anticoagulation treatment. Then, multivariate logistic regression analysis was performed to identify independent clinical predictors of long-term anticoagulation therapy planned for >12 months. Univariate predictors with a p-value <0.05 were included in the regression model; a backward elimination procedure was used to discard stepwise variables without significance from the model.

Cox regression analyses reporting hazard ratios (HR) and 95% CIs were performed for comparing clinical outcomes between various patient groups. All reported p-values are two tailed. Data were analyzed using STATA 10 software (STATACorp LP, College Station, TX, USA).

Results

Patient characteristics

Overall, 1,247 patients were enrolled; 315 (25%) had cancer and 932 (75%) had no cancer (▶Table 1). Among 315 cancer patients, 179 (57%) had metastatic disease, 154 (49%) had recent and 114 (36%) ongoing chemotherapy, 83 (26%) had cancer surgery within six months and 35 (11%) had cancer surgery within 30 days, 22 (7%) were admitted to the intensive care unit (ICU), and 63 (20%) had prior VTE.

Acute PE alone was diagnosed in 117 (37%) patients with cancer and 300 (32%) patients without cancer (p=0.11), DVT alone in 155 (49%) and 448 (48%) (p=0.73), and PE plus DVT in 43 (14%) and 184 (20%) patients (p=0.015), respectively. Overall, 421 (34%) had clinically massive VTE of whom 39 (9%) had massive PE, defined as presence of systemic systolic pressure <90 mmHg or cardiogenic shock, and 382 (91%) massive DVT, defined as swelling, discomfort, and impaired mobility of the entire leg. The proportion of patients with clinically massive VTE was similar in patients with and without cancer (35% vs. 33%; p=0.52). In total, 181 (15%) patients had isolated distal DVT, and 77 (6%) upper extremity DVT; patients with cancer more often had upper extremity DVT (15% vs. 5%; p<0.001), and less often had isolated distal DVT (10% vs. 16%; p=0.019) than those without cancer.

Clinical outcomes at 30 days

The presence of cancer was associated with an increased risk of 30-day mortality (11.4% vs. 2.1%; HR 5.10, 95% CI 2.57–10.13; p<0.001) (▶Fig. 1) or combined death or recurrent VTE at 30 days (13.2% vs. 4.5%; HR 2.91, 95% CI 1.70–4.99; p<0.001). Bleeding complications requiring medical attention at 30 days were similar between patients with and without cancer (7.2% vs. 6.0%; HR 1.09, 95% CI 0.59–2.00; p=0.79).

In patients with cancer, neither the presence of metastases (14.3% vs. 6.5%; HR 1.86, 95% CI 0.78–4.44; p=0.15) nor prior VTE (6.2% vs. 12.6%; HR 0.52, 95% CI 0.16–1.74; p=0.28) were associated with an increased risk of 30-day mortality.

Overall, the risk of 30-day mortality was similar in patients with planned long-term vs. limited-duration anticoagulation treatment (6.1% vs. 4.6%; HR 1.28, 95% CI 0.65–2.50; p=0.47); with similar findings in the subgroup of patients with cancer (9.3% vs. 13.4%; HR 0.64, 95% CI 0.29–1.40; p=0.26) and without cancer (2.0% vs. 2.1%; HR 1.32, 95% CI 0.36–4.88; p=0.68).

Planned initial and long-term treatment of VTE

Overall, antithrombotic therapy was initiated on an inpatient basis in 71% patients with and in 62% patients without cancer (p=0.007). Among 644 patients with acute PE, the frequency of in-hospital treatment was similar in patients with and without cancer (88% vs. 87%; p=0.81); and among 603 patients with acute DVT alone, it was higher in patients with cancer than in those without cancer (53% vs. 35%; p<0.001).

In comparison to patients without cancer, long-term LMWH mono-therapy was planned more frequently in patients with

cancer (39% vs. 9%; p<0.001), and cancer patients used VKA at any time less frequently (51% vs. 87%; p<0.001). In patients on LMWH mono-therapy, treatment duration of at least three months was planned in 87% of cancer patients versus 67% of non-cancer patients (p=0.001). In comparison to patients without cancer, long-term anticoagulation treatment for >12 months was more often planned in patients with cancer-associated VTE (47% vs. 19%; p<0.001) (▶ Fig. 2). Long-term anticoagulation was more often planned in cancer patients with recurrent versus first VTE (70% vs. 41%; p<0.001), with metastatic versus non-metastatic disease (59% vs. 31%; p<0.001), and with recent or ongoing chemotherapy versus no chemotherapy (54% vs. 40%; p=0.020), as well as in those treated in academic versus non-academic hospitals (52% vs. 40%; p=0.039). Long-term anticoagulation therapy was similarly often planned in cancer patients with versus without surgery (44% vs. 48%; p=0.48). Among patients without cancer, long-term anticoagulation was planned in 53% with recurrent VTE versus 8% patients with first VTE (p<0.001), and in 21% with proximal DVT versus 9% patients with isolated distal DVT (p=0.002). Overall, there was a trend towards more frequent planning of long-term anticoagulation treatment for more than 12 months in patients with versus without clinically massive VTE (29% vs. 24%; p=0.057).

Mechanical therapy with vascular compression stockings or bandages was prescribed in 85% patients with and 82% patients without cancer (p=0.19), and inferior vena cava (IVC) filters were used in 2% patients without and 1% patients with cancer (p=0.11). Among 52 (17%) cancer patients with an increased risk of bleeding, including patients with recent bleeding requiring medical attention, low platelet count <100,000 per ml, or renal failure with creatinin clearance <30 ml/minute, LMWH mono-therapy was planned in 40%, VKA therapy in 46%, and long-term anticoagulation treatment for >12 months in 50%.

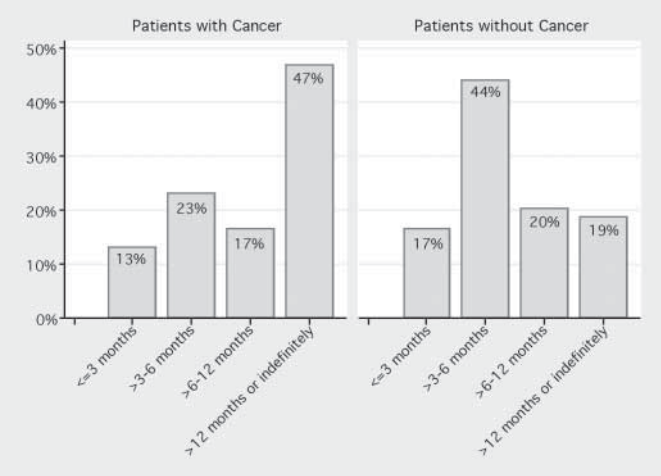

Figure 2: Planned duration of anticoagulation therapy in patients with and without cancer.

Predictors of planned indefinite-duration anticoagulation treatment

In patients with cancer, the strongest univariate factors associated with a planned long-term anticoagulation therapy were prior VTE, metastatic disease, and ongoing or recent chemotherapy whereas

Table 2: Clinical factors associated with planned long-term anticoagulation therapy.

	Univariate analysis			Multivariate analysis		
Factor	**OR**	**95% CI**	**P**	**OR**	**95% CI**	**P**
Patients with cancer						
Prior VTE	3.30	1.82–6.00	<0.001	3.46	1.83–6.53	<0.001
Metastatic disease	2.90	1.73–4.88	<0.001	3.04	1.86–4.97	<0.001
Ongoing or recent chemotherapy	1.70	1.08–2.65	0.020			
Acute infection including sepsis	0.33	0.17–0.67	0.002	0.28	0.13–0.61	0.001
ICU admission	0.23	0.08–0.70	0.009			
Patients without cancer						
Prior VTE	13.55	9.27–19.81	<0.001	15.62	10.48–23.30	<0.001
Acute respiratory failure	2.09	1.15–3.81	0.016	2.40	1.15–4.91	0.019
History of stroke/TIA	1.88	1.00–3.51	0.049			
Age >65 years	1.41	1.01–1.96	0.042			
Pulmonary embolism	1.30	1.01–1.66	0.040	1.70	1.09–2.63	0.018
Provoked VTE	0.62	0.43–0.89	0.009			
Isolated distal DVT	0.40	0.23–0.72	0.002	0.40	0.20–0.80	0.010

OR, odds ratio; CI, confidence interval; VTE, venous thromboembolism; DVT, deep-vein thrombosis; ICU, intensive care unit; TIA, transient ischaemic attack.

acute infection and admission to the intensive care unit were inversely associated with it (▶Table 2). Recurrent VTE, metastatic disease, and the absence of an acute infection were independently associated with the intention to maintain anticoagulation for more than 12 months.

In patients without cancer, prior VTE, acute respiratory failure, history of stroke, age >65, and PE were univariately associated with a planned long-term anticoagulation therapy but provoked VTE and isolated distal DVT were inversely related with it (▶Table 2). Prior VTE, acute respiratory failure, PE, and thrombosis localisation other than isolated distal DVT were independently associated with the intention to maintain anticoagulation for more than 12 months.

Discussion

In the prospective Swiss Venous Thromboembolism Registry (SWIVTER) II, less than half of the patients with acute cancer-associated VTE were planned for long-term anticoagulation treatment of more than 12 months. Prior VTE, metastatic disease, and the absence of acute infection were independently associated with the intention to maintain anticoagulation therapy for >12 months. Surprisingly, the majority of patients with first cancer-associated VTE or with non-metastatic cancer had a plan for limited-duration anticoagulation therapy of no more than 12 months. As expected, provoked VTE, thrombosis localisation other than isolated distal DVT, and the presence of PE predicted the duration of anticoagulation treatment in patients without cancer. Among the cancer patients treated with LMWH mono-therapy in the present study, 87% had a planned treatment of at least three months. This rate was lower (65%) in cancer patients treated on an outpatients basis for acute DVT from the Outpatient Management of Thrombosis in Switzerland (OTIS-DVT) Registry (15).

The finding that patients with cancer did not develop clinically massive VTE more often than patients without cancer is in accordance with the U.S. American DVT FREE Registry where cancer did not predict massive DVT (16). In patients with acute VTE, the presence of cancer, particularly metastatic disease, is associated with an increased risk of VTE recurrence and mortality (4, 5, 10, 11). The reported associations of metastatic disease and prior VTE with 30-day outcomes in our study had large confidence intervals and should therefore be interpreted with caution.

Considerable inconsistency in the planning of the duration of anticoagulation treatment has previously been reported in patients with acute VTE. The Multicenter Advanced Study for a Thromboembolism Registry (MASTER) enrolled 2,119 patients with acute VTE of whom 20% had cancer (17). Similarly to our study, patients with cancer were more often hospitalised (71% vs. 62% in SWIVTER II, 73% vs. 67% in MASTER) and less often received oral anticoagulation (51% vs. 87% in SWIVTER II, 64% vs. 82% in MASTER) than patients without cancer. The Outpatient Treatment of Deep Vein Thrombosis in Switzerland (OTIS-DVT) registry showed that only 40% of outpatients with unprovoked proximal, unprovoked recurrent, or cancer-associated DVT had a planned anticoagulation treatment for an indefinite period (18). SWIVTER II is the first national survey reporting on the duration of anticoagulation treatment specifically for patients with cancer-associated VTE according to current consensus guidelines of the American College of Chest Physicians (13) and the American Society of Clinical Oncology (14).

We may only speculate about reasons for the observed lack of long-term secondary prophylaxis in patients with cancer-associated VTE, owing to the fact that these patients are at high risk of VTE recurrence as well as bleeding complications (10, 12, 19). However, long-term anticoagulation was planned similarly often in cancer patients with an increased risk of bleeding (50%) when compared with the entire cohort of patients with cancer (47%). Other factors that may explain the low rates of planned long-term anticoagulation therapy include cancer prognosis (e.g. terminal cancer), intended cancer cure, possible interaction of oral anticoagulants with chemotherapy or other co-medications, low awareness of the risk of thrombosis recurrence, unawareness of current guideline recommendations, patient preferences, the need for anticoagulation monitoring, and health care cost constraints.

The strength of our study is the prospective multicentre enrolment of consecutive patients with acute VTE and the collection of detailed information on VTE diagnosis, VTE risk factors, planned duration of pharmacological therapy, and 30-day clinical outcomes. A weakness of the study is that no information on i) the specific reasons for selecting the duration of anticoagulation treatment, ii) patient compliance, and iii) actual duration of anticoagulation treatment was collected. It is likely that a substantial proportion of patients have not received long-term anticoagulation treatment according to the initial plan because of intercurrent bleeding complications during anticoagulation therapy, problems with international normalised ratio monitoring, cancer cure, or terminal cancer care with comfort measures only. Conversely, the plan to initiate anticoagulation therapy for a limited duration may have been changed to an indefinite-duration because of recurrent thrombotic events in several cancer patients. Finally, our findings may not necessarily be generalisable to other countries.

What is known about this topic?

- Venous thromboembolism (VTE) represents the second leading cause of death in cancer patients, and it is a significant predictor of mortality in hospitalised patients with cancer.
- In patients with cancer-associated VTE, current consensus guidelines recommend anticoagulation therapy for an indefinite duration or until the cancer is resolved.

What does this paper add?

- Long-term anticoagulation treatment for more than 12 months was planned in less than half of the cancer patients with acute VTE.
- The low rates of long-term anticoagulation in cancer patients with a first episode of VTE and in patients with non-metastatic cancer require particular attention.

In summary, long-term anticoagulation treatment was planned in less than half of the cancer patients with acute VTE. The low rates of long-term anticoagulation in cancer patients with a first episode of VTE and in patients with non-metastatic cancer require particular attention.

Acknowledgement

We thank following site investigators for the participation in the study: Marietta Puck (University Hospital Zurich), Jörg Ugi (University Hospital Bern), Daniel Hayoz (Cantonal Hospital Fribourg), Peter Rupp (Salem Hospital Bern), Thomas Baldi (University Hospital Basel), Alexander Imhof (Regional Hospital Langenthal), Anita Lebeda (Cantonal Hospital Frauenfeld), Michaela Heidemann-Zabel (Cantonal Hospital Lucerne), Stephanie Witzig (University Hospital Lausanne), Robert Escher (Regional Hospital Burgdorf), Barbara Federspiel (Hospital Zimmerberg Wädenswil), Thierry Fumeaux (Regional Hospital Nyon), Ulrich Frank (Cantonal Hospital Chur), Thomas Kaeslin (Cantonal Hospital Sarnen), Andreas Walser (Regional Hospital Flawil), Heinz Josef Schaad (Regional Hospital Interlaken), Urs Marbet (Cantonal Hospital Altdorf), Herve Duplain (Regional Hospital Porrentruy).

Conflict of interest

This study was supported by Sanofi-Aventis (Suisse) SA, Meyrin, Switzerland. Data collection, data management, and analysis were independent from the sponsor. Dr. Spirk is an employee of Sanofi-Aventis (Suisse) SA, Meyrin, Switzerland.

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