Mitomycin C, Vinblastine, and Carboplatin Regimen in Patients with Nonsmall Cell Lung Cancer

A Phase II Trial

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Data have been previously published in abstract form in Paccagnella A, Favaretto A, Oniga F, Festi G, Lauro S, Morabito A, et al. MVC regimen in nonsmall cell lung cancer. A Phase II trial of mitomycin C, vinblastine, and carboplatin [abstract 1129]. *Proc Am Soc Clin Oncol* 1995;14:367.

Supported in part by CNR Grant 92.02340.PF39 and AIRC (Associazione Italiana per la Ricerca sul Cancro) Milano.

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Received December 26, 1995; revisions received April 24, 1996, and June 27, 1996; accepted June 27, 1996.

BACKGROUND. The mitomycin C, vinblastine, and cisplatin (MVP) combination is one of the most frequently used in the palliative setting, but it produces considerable toxicity. Carboplatin and cisplatin have different patterns of toxicity. The goal of this study was to evaluate a combination similar to MVP, using carboplatin instead of cisplatin to render it more feasible in an outpatient setting.

METHODS. Inclusion criteria for this study included: inoperable patients or patients relapsing after previous surgery, with nonsmall cell lung carcinoma (NSCLC), a performance status (PS) >50%, and no previous chemotherapy. The chemotherapy regimen included carboplatin, 300 mg/m^2 on Day 1; mitomycin, 8 mg/m^2 on Day 1; and vinblastine, 4 mg/m^2 on Days 1, 8, and 15 (on Day 15 vinblastine was delivered only in the first cycle) (MVC) every 3 weeks for at least 3 cycles.

RESULTS. From August 1991 until August 1994, 70 patients entered the trial. All were evaluable for toxicity and response. The median age was 62 years (range, 40–73 years). The male/female ratio was 60:10 (86%:14%); the ratio of Stage III to Stage IV disease was 26:44 (37%:63%); and the ratio of PS $>$ 70 to $\leq$ 70 was 49:21. A total of 296 cycles (median, 4 [range, 1–6 cycles] per patient) were delivered, 280 of 296 (95%) in an outpatient setting with only 4 patients requiring hospitalization for treatment delivery. Overall response rate (RR) was 38.6% (95% confidence interval [CI], 27–51%) (1 complete response, 1.5%; 26 partial responses, 37.1%). Median duration of response was 9.8 months (range, 2–27 months). In Stage III patients the RR was 42% and in Stage IV patients it was 34%. Overall median survival was 9.5 months (95% CI, 6.8–15.3 months). Survival at 1 year was 39% (standard error [SE] 3.6%) and was 11% at 2 years (SE 3.6%). In Stage III patients median survival was 13 months and the 1-year survival rate was 54% (SE 10%); Stage IV patients had a median survival of 7.4 months and a 1-year survival rate of 28% (SE 7%). Delivered dose intensity was: carboplatin, 71%; vinblastine, 60%; and mitomycin C, 77% of the planned dose intensity. The back calculation of carboplatin area under the curve (AUC) with Calvert's formula and with the Cockcroft-Gault glomerular filtration rate estimation, showed a median AUC value of 4 (range, 2–8). Using the more precise Chatelut formula, AUC was again 4 (range, 2–7). Hematologic toxicity was the major side effect; Grades 3 and 4 leukopenia were observed in 34% and 6% of patients, respectively, and Grades 3 and 4 thrombocytopenia in 25% and 4% of patients, respectively. Grade 2 infection occurred in 10% of patients, with only 1 case of sepsis; severe constipation and Grade 2 alopecia occurred in only 1 patient; and no case of higher than Grade 1 nephrotoxicity was observed. No pulmonary toxicity was observed. Compliance with treatment was good with only one patient refusal after the first cycle.

CONCLUSIONS. Chemotherapy for advanced NSCLS is still controversial, because effectiveness in terms of RR and symptom control must be weighed against treatment toxicity and costs. From our study it appears that MVC is easy to deliver in an outpatient setting, and has good patient compliance, low toxicity profile, and

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promising RR and response duration. The substitution of carboplatin for cisplatin in regimens for advanced NSCLC should be considered. *Cancer* 1996; 78:1701–7.
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KEYWORDS: carboplatin in combination, nonsmall cell lung carcinoma, effectiveness, toxicity profile.

In advanced stage (IIIB-IV) nonsmall cell lung carcinoma (NSCLC), the role of chemotherapy is still controversial.[1] The more active combinations include cisplatin and can produce a response rate between 20% and 60%. Factors affecting the achievement of an objective response are related to initial performance status (PS), stage of disease, weight loss, and previous treatment.[2] It has not yet been clearly established whether regimens with cisplatin at doses of approximately 100 to 120 mg/m^2 are more effective than regimens with a lower dosage (50–60 mg/m^2).[3] It appears that combinations containing cisplatin at doses higher than 100–120 mg/m^2 are not able to further increase the response rate.[4] Cisplatin and carboplatin act with the same active metabolite. However, they show a different pattern of toxicity. Carboplatin presents a greater hematologic toxicity but is better tolerated overall than cisplatin, because it presents a reduced renal, gastrointestinal, neurologic, and otologic toxicity. Its easier modality of administration also makes it more suitable in an outpatient setting. The equivalent doses of cisplatin and carboplatin are between 1:3.5 and 1:4.[4] In patients with ovarian carcinoma, randomized studies comparing the same combinations, including cisplatin, 100 mg/m^2 or carboplatin, 300 mg/m^2, showed similar response rates and overall survival.[5,6] One of the most frequently adopted regimens in NSCLC is mitomycin C, vindesine or vinblastine, and cisplatin (MVP). In its various formulations (mitomycin, 6–8 mg/m^2; vindesine or vinblastine, 3–4 mg/m^2, and cisplatin, 100–120 mg/m^2), it can produce a response rate between 20% and 75%.[7–11] In patients with widespread disease, the role of chemotherapy is currently restricted to palliation. To minimize the subjective and objective toxicity of chemotherapy and to increase treatment feasibility in an outpatient setting, a Phase II trial with a regimen similar to MVP but including carboplatin at a dose of 300 mg/m^2 instead of cisplatin (MVC), was started.

PATIENTS AND METHODS

Patient Eligibility and Evaluation

Patients were required to have histologically confirmed NSCLC, measurable or evaluable lesions, recurrence after previous surgery or radiation therapy or any other condition not amenable to curative surgery, a Karnofsky PS greater than 50%, normal renal, hepatic, and hemopoietic functions, no previous chemotherapy, physiologic age younger than 70 years, a life expectancy of more than 3 months, and informed consent. Staging procedures included chest radiograph, bronchoscopy, chest computed tomography (CT) scan, brain and upper abdomen CT scan or sonography and bone scan, and blood and urine chemistry. Before each course of treatment, a complete physical examination was repeated and disease- and treatment-related symptoms were carefully recorded. A chest radiograph was obtained every 3 weeks. Tests for measurable or evaluable disease parameters were repeated at 9 weeks from initiation of chemotherapy and at the end of planned chemotherapy for nonprogressing patients. A complete response was defined as the disappearance of all clinical and radiologic evidence of disease accompanied by subjective improvement, and required bronchoscopic confirmation. A partial response (PR) was defined as a greater than 50% decrease of all measurable disease, or an estimated decrease in tumor size of 50% or more for nonmeasurable disease, with no evidence of new lesions, lasting for at least 4 weeks. Minor responses or unchanged disease after three courses were accepted as treatment failure. Patients lost to follow-up after the first cycle were considered treatment failures. Previously irradiated areas and pleural effusions were considered unevaluable. Response duration was defined as the time from the beginning of chemotherapy to first evidence of relapse or progression. Overall survival was estimated by the Kaplan–Meier method.

Treatment and Study Design

All patients received the following combination chemotherapy: carboplatin, 300 mg/m^2 intravenously on Day 1; mitomycin C, 8 mg/m^2 on Day 1; and vinblastine, 4 mg/m^2 on Days 1, 8, and 15 (on Day 15 vinblastine was delivered only in the first cycle). As antiemetic treatment, combinations including high dose methylprednisolone (125 to 250 mg/m^2) were routinely used. The regimen was recycled every 3 weeks for at least 3 cycles. Responding patients were treated for a maximum of six cycles. Hematologic toxicity was evaluated weekly. Nonhematologic toxicity was evaluated before each chemotherapy administration according to the

World Health Organization (WHO) criteria. Criteria for removal from the study were disease progression, development of intolerable toxicity defined as nonhematologic Grade 4 toxicity (Grade 3 for neurotoxicity and ototoxicity), Grade 4 hematologic toxicity evaluated at Day 21 and persisting for more than 1 week; and patient withdrawal of consent.

When the leucocyte count was less than 3500 per microliters and platelets were less than 120,000 at Day 21, the treatment was delayed for 1 week. When the leukocyte count was less than 2500 and platelets were less than 50,000 on Days 8 or 15, vinblastine was not administered. In instances of Grades 1 and 2 peripheral neuropathy, the vinblastine dose was reduced by 50%. Patients with limited disease, suitable for radiation treatment, received thoracic radiotherapy at the end of chemotherapy.

Calculation of Dose Intensity

Dose intensity (DI) was calculated according to Longo et al.[12] We calculated DI truncating treatment to the first four cycles, because we planned four cycles of treatment. Only responding patients received more than four cycles. The DI in milligrams per square meter per week for a particular agent was calculated for each patient by the following formula:

$$\frac{\text{Total milligrams of drug in 4 cycles per body surface area}}{\text{Total days of therapy}/7},$$

in which total days of therapy was the number of days between Cycle 1, Day 1, and Cycle 4, Day 22 (or Cycle 5, Day 1 for patients who received more than 4 cycles). Average DI for each drug was calculated by averaging the DI values for individual patients. The average percent of projected dose was calculated by averaging the percent of projected dose for individual patients for each drug.

Calculation of Area Under the Time/Concentration Curve (AUC)

The carboplatin plasma concentration versus time expressed as the AUC was backcalculated according to the formula proposed by Calvert et al.[13] The glomerular filtration rate (GFR) was established using the Cockcroft–Gault formula.[14] Calvert formula: AUC = dose/(GFR + 25) Cockcroft–Gault formula: GFR = (1.23 × (140 − age) × weight)/creatinine (age in years, weight in kilograms, creatinine expressed in micromolar concentration; female: × 0.85).

For a more precise AUC estimation the Chatelut formula was also used.[15] Chatelut formula: carboplatin clearance = weight X 0.134 + [218 X weight X (1-0.00457 X age) X (1-0.314 X sex)]/creatinine; (with creatinine expressed in micromolar concentration, weight in kilograms, age in years, and sex = 0 if male and = 1 if female). AUC = dose/clearance.

TABLE 1
Patient Characteristics

		No.	%
Total patients enrolled		70	
Median age at diagnosis (range) (yrs)		62	(40–73)
Sex	Males	60	86%
	Females	10	14%
Stage	IIIA	2	3%
	IIIB	24	34%
	IV	44	63%
Histology	Epidermoid	23	33%
	Adenocarcinoma	42	60%
	Large cell, undiff.	5	7%
PS	>70	49	70%
	≤70	21	30%
Disease	Measureable	62	89%
	Evaluable	8	11%
Pretreatment	Yes (surg/RT)	10	14%
	No	60	86%

Undiff.: undifferentiated; PS: performance status; surg: surgery; RT: radiation therapy.

RESULTS

Patient Characteristics

Between August 1991 and August 1994, 70 patients were entered into the study. All patients were evaluable for toxicity and response. Three patients (4%) with inadequate documentation of response were considered nonresponders. The characteristics of the 70 patients are summarized in Table 1. The majority of patients had disseminated disease (65%), adenocarcinoma histologic subtype (60%), and a Karnofsky PS of more than 70 (70%). Approximately 11% of the patients were pretreated with radiation therapy or surgery.

Response and Survival

Only one patient obtained a complete response (1.5%) and this patient had limited disease; 26 other patients (37.1%) obtained a PR for an overall response rate of 38.6% (95% confidence interval [CI], 27–51%) (Table 2). Response rate was slightly higher in patients with limited disease (42%; 95% CI, 23–63%) compared with patients with disseminated disease (34%; 95% CI, 20–50%). Eight patients (11%) had a minor response, and 21 (30%) had stable disease. Only 14 patients (20%) progressed during treatment. The median response duration was 9.8 months (range, 2–27 months). For Stage III patients, median duration of response was 13 months; Stage IV patients had a median duration

TABLE 2
Mitomycin C, Vinblastine, and Carboplatin

Response	No. of patients	%
CR	1	1.5%
PR	26	37.1%
OR	27	38.6%[a]
NC	29	41.4%
PD	14	20%

CR: complete response; PR: partial response; OR: overall response; NC: no change; PD: progressive disease.

[a] 95% confidence limits: 27–51%. Response duration: median: 9.8 months (range, 2–27 months).

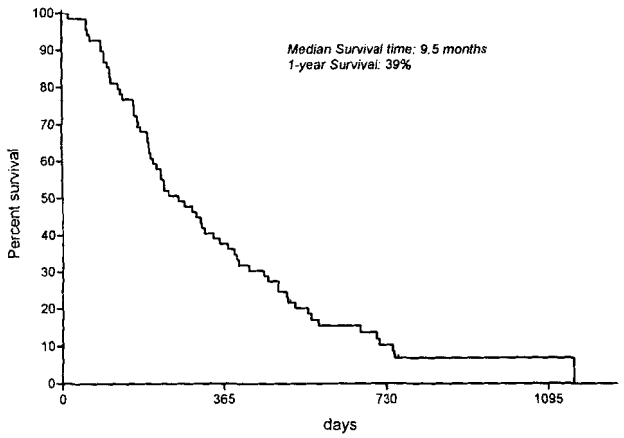

FIGURE 1. Kaplan–Meier estimation of overall survival for the 70 patients.

of response of 6 months. The overall median survival was 9.5 months (range, 6.8–15.3 months, 95% CI). As shown in Figure 1, survival at 1 year was 39% (standard error [SE], 3.6%) and at 2 years was 11% (SE, 3.6%). In Stage III patients, median survival was 12.8 months; 1-year and 2-year survival rate were, respectively, 50% (SE, 9%) and 14% (SE, 7%). Stage IV patients had a median survival of 7.3 months, and 1-year and 2-year survival rates of, respectively, 28% (SE, 6%) and 8% (SE, 4%). Of the 26 Stage III patients, 8 patients (30%) who did not progress during chemotherapy received subsequent radical thoracic radiotherapy.

Dose Analysis and Toxicity

A total of 296 cycles was delivered with a median of 4 (range, 1–6 cycles) per patient. All 27 responding patients were able to receive the planned cycles. Only two patients refused chemotherapy, one after the first cycle and one after three cycles. Because of planned dose reductions or delays due to toxicity, the delivered DI of carboplatin was 71 mg/m^2/week, which represents 71% of the planned DI (100 mg/m^2/week). The delivered DI of vinblastine was 1.8 mg/m^2/week, 60% of the planned DI (3 mg/m^2/week); the delivered DI of mitomycin C was 2.05 mg/m^2/week, 77% of the planned DI (2.6 mg/m^2/week). We calculated the delivered DI on the first 4 cycles (i.e., on 236 of 296 delivered cycles) because only responding patients had more than 4 cycles. The carboplatin AUC of the first cycle was backcalculated using Calvert's classic formula.[13] Because no ^{51}Cr-ethylenediamine tetraacetic acid (EDTA) clearance was planned and because a direct measurement of creatinine clearance was not performed in all patients, the GFR was derived by using the Cockcroft–Gault serum creatinine-based formula.[14] The median obtained AUC was 4 (range, 2–8) with only 16% of patients having an AUC of 3 or less and 45% of patients having an AUC of 5 or more. When the AUC was calculated according to the method recently proposed by Chatelut, the median was again 4 (range, 2–7).[15] However, it is interesting to note that a greater proportion of patients received an AUC $\leq$ 3 (45%) and that only 23% of patients received an AUC $\geq$ 5. Two hundred and eighty cycles of 296 (95%) were delivered in an outpatient setting, with only 4 patients requiring hospitalization for treatment delivery. The occurrence of different types and degrees of toxicity is shown in Tables 3 and 4.

TABLE 3
Hematologic Toxicity by Patient

WHO grade	1	2	3	4
Leukopenia	13 (19%)	18 (27%)	23 (34%)	4 (6%)
Thrombocytopenia	14 (21%)	8 (12%)	17 (25%)	3 (4%)
Anemia	19 (28%)	18 (27%)	14 (21%)	2 (3%)

WHO: World Health Organization.

TABLE 4
Nonhematologic Toxicity by Patient

WHO grade	1	2	3	4
Gastrointestinal				
Nausea/vomiting	10 (14%)	2 (3%)	1 (1.4%)	—
Mucositis	8 (11%)	2 (3%)	—	—
Nephrotoxicity	1 (1.4%)	—	—	—
Alopecia	5 (7%)	1 (1.4%)	—	—
Infection	14 (20%)	7 (10%)	—	—
Neurotoxicity				
Peripheral	11 (16%)	—	—	—
Constipation	14 (20%)	1 (1.4%)	1 (1.4%)	—
Asthenia	21 (30%)	3 (4%)	1 (1.4%)	—

WHO: World Health Organization.

Hematologic toxicity, calculated at the nadir, was the most frequent side effect; 24% of patients experienced greater than Grade 2 anemia (i.e, hemoglobin < 7.9 g/dL). Blood transfusions were required in 15 patients (21%). The most frequent hematologic toxicity was leukopenia, with 40% of patients experiencing greater than Grade 2 leukopenia (i.e., a leukocyte count $< 1900/\mu L$) evaluated at the nadir. However, only 4 patients (6%) had Grade 4 leukopenia (i.e., leukocyte count $< 1000/\mu L$). In all 4 patients, it lasted for more than 1 week and required granulocyte-colony stimulating factor (G-CSF) support. Thrombocytopenia was less frequent, with only 29% of patients showing a greater than Grade 2 toxicity (i.e., platelets $< 49.000/\mu L$). In no patient was a platelet transfusion required. No Grade 4 nonhematologic toxicity was observed. Only one patient had Grade 3 neurologic toxicity (i.e., severe constipation requiring daily specific therapy). Another patient had a Grade 1 renal toxicity (i.e., creatinine $> 1.25 \times$ upper normal value). No patients showed clear signs of pulmonary toxicity, although mitomycin C was used in every cycle. It is interesting to note that the mitomycin C delivered total dose was 79% of the planned total dose. Four patients required hospitalization during treatment. One was hospitalized for hematologic and nonhematologic toxicity requiring supportive treatment, two were hospitalized for supportive treatment for a nonchemotherapy-related preexisting cardiomyopathy, and one was hospitalized for an exacerbation of a duodenal ulcer. No treatment-related deaths were observed.

DISCUSSION

The value of chemotherapy in advanced NSCLC is still debated. Many clinicians prefer not to submit patients to chemotherapy because of concern about chemotherapy toxicity with no clear benefit in terms of survival.[16] Recently, however, Stewart et al. published a meta-analysis of studies comparing best supportive treatment versus the same plus chemotherapy, and showing a small but definite advantage in median survival for patients with advanced NSCLC receiving cisplatin-containing combinations.[17] As might be expected, no long term survival advantage was observed, however. Although this is an important achievement from an explanatory point of view, it is likely that clinicians will remain reluctant to treat this subset of patients with chemotherapy because of the substantial toxicity induced by cisplatin-containing regimens. The availability of new, effective, but expensive antiemetic treatments is unlikely to substantially modify this attitude. However, it should be emphasized that with the most frequently adopted combinations, such as MVP, mitomycin C, ifosfamide and cisplatin, cisplatin/etoposide, chemotherapy can produce a good symptom palliation not only in patients obtaining an objective response but also in patients only obtaining minor responses.[18] With a modified version of MVP (cisplatin at 50 mg/m^2), Nicolson et al.[10] obtained a 31% response rate in 84 patients (23 Stage IIIB and 61 Stage IV). Symptom relief was obtained in 96% of responding patients and in 34% of patients with minor response or stable disease.[10] The new drugs or combinations, currently under Phase I and II experimentation, appear unlikely to modify the outcome of advanced NSCLC in comparison with the best available combinations. It would therefore seem reasonable to modify one of the most used regimens (MVP), substituting cisplatin with carboplatin to reduce the nonhematologic side effects of the combination and thus increase the feasibility of treatment in an outpatient setting.

Carboplatin is believed to be most appropriately dosed using AUC.[19] In patients with normal renal function, the 300 mg/m^2 dose adopted in the MVC regimen could probably result in considerable underdosage. Currently, calculation of patient specific carboplatin doses is most commonly done by the Calvert formula.[13] The limited availability of ^{51}Cr-EDTA clearance as well as the difficulties of obtaining a reliable collection of a 24-hour creatinine clearance to assess the GFR tend to limit the use of Calvert's proposed method for individual assessment of carboplatin dosages. Conversely, the widely adopted estimation of GFR according to the formula proposed by Cockcroft and Gault could lead to considerable bias and result in the patient being exposed to a lower than desired AUC, with variations as high as to 40%.[15,19–21] Moreover, this variation tends to increase with the cycles delivered.[20] We therefore chose to calculate the individual carboplatin dosages in mg/m^2. Recently, Chatelut et al.[15] proposed a new formula to assess carboplatin clearance and the relative AUC. With this method, the individual carboplatin dosages were as accurate as the ones obtained by Calvert et al.[13] using the ^{51}Cr-EDTA method.[15] In the current study, the AUC was backcalculated by Calvert's method, estimating the GFR according to Cockcroft-Gault,[14] and with Chatelut's method.[15] We obtained the same median delivered AUC, respectively, of 4 (range, 2–8) and 4 (range, 2–7). However, it is interesting to note that the proportion of patients receiving an AUC ≤ 3 was 16% and 45%, respectively, and the proportion of patients receiving an AUC ≥ 5 was 45% and 23%, respectively. The AUC data obtained with Chatelut's formula appears to clearly indicate that we underdosed with carboplatin, and could explain the limited hematologic toxicity experienced with MVC.

The response rate (38.6%), the response duration

(9.8 months), and overall median survival (9.5 months) obtained with MVC in this Phase II trial are, however, similar to those previously obtained with MVP in 35 patients with similar characteristics, and to those reported in the literature.[8,9,11] It is noteworthy that the median (9.5 months) and 1-year survival (39%) compare favorably with survival calculated in similar patient populations treated with cisplatin-containing combinations. This is particularly evident when Stage III and Stage IV patients are analyzed separately (median and 1-year survival of 13 and 7.4 months and 54% and 20%, respectively).

In this trial, a good patient compliance to MVC was also observed. The nonhematologic toxicity was usually mild and transient. The hematologic toxicity was quickly reverted, with only three patients requiring G-CSF support for prolonged leukopenia. Fifteen patients (21%) required blood transfusions for anemia but only 1 patient was hospitalized for a septic fever requiring intensive support. It is noteworthy that no patients experienced pulmonary toxicity, as would normally be expected when mitomycin C is used in every cycle. This is probably because the administration of mitomycin C was preceded by high doses of methylprednisone as a standard component of our antiemetic treatment. It has been suggested that with steroid premedication pulmonary complications are unusual.[22] No toxic deaths were observed. All patients were treated in an outpatient setting. Because hospitalization has been identified as one of the major determinants of high treatment costs for advanced NSCLC, this carboplatin modification of the MVP regimen seems particularly promising also from the point of view of cost.[23] From these data, it appears that MVC is a promising regimen, as an alternative to MVP or other cisplatinum-based combinations, in palliation treatment of advanced NSCLC.[24-27]

The data available from literature on the role of carboplatin in combination for NSCLC treatment are controversial. To our knowledge, only two trials compare carboplatin with cisplatin in the treatment of NSCLC. In a randomized trial comparing cisplatin plus etoposide with carboplatin plus etoposide, Klastersky et al. obtained a similar response rate and survival duration, with an increased hematologic and nonhematologic toxicity for the cisplatin combination.[28] Another randomized trial conducted by the Eastern Cooperative Oncology Group showed a significantly improved survival and a decreased toxicity for single agent carboplatin in comparison with MVP and other cisplatin-based combinations.[29]

Because cisplatin-containing combinations represent the standard regimens in chemotherapy treatment of advanced NSCLC,[17] we started a Phase III trial in January 1995 comparing MVP with MVC, with quality of life evaluation as the primary study endpoint, and response rate, response duration, and survival as subsidiary endpoints.

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