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CLINICAL PROFILE OF DRUG RESISTANT TB PATIENTS WITH SPECIAL REFERENCE TO BEDAQUILINE THERAPY AND ITS COMPLICATIONS IN A TERTIARY CARE HOSPITAL IN WEST-BENGAL- A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Background: Tuberculosis (TB) is a global disease and is the leading infectious cause of death worldwide. Drug-resistant TB (DRTB) can occur when the drugs used to treat TB are misused or mismanaged. The programmatic management of drug-resistant TB (PMDT) is providing services based in the TB strategy in order to achieve the targets set for drug-resistant TB in the Global Plan to Stop TB. Bedaquiline (Bdq) is a novel drug with strong bactericidal action got nationwide access in PMDT guideline in 2018 by WHO and now being used in the first six months of all oral longer DRTB regimen. This study aims to assess the prevalence of patients taking Bedaquiline containing all oral longer MDR-TB regimen and the incidence of Bedaquiline induced complications among those patients. **Materials And Method:** A total of 100 DRTB patients who are attending our study area were included at random. After inclusion into this study, patients were evaluated on the basis of a) detailed history and clinical examination and b) baseline investigations and other investigations as found necessary. On the basis of LPA, they were categorized as resistance to first or second line ATDs. Then 40 of them were put on Bedaquiline containing regimen and any undesired effects arising out of Bedaquiline were closely looked for. **Results:** Out of 100 DRTB patients (of which 70% were males), 35 patients exhibited resistance to first line ATD and the rest 65 patients to second line ATD via LPA. Maximum number of DRTB patients were from the age group 25-40 years. Total 40 patients were put on Bedaquiline containing regimen of which only 7 of them (17.5%) developed some complications. Nausea and joint pain were main complaints. **Conclusion:** DRTB is a global concern and Bedaquiline, because of its strong bactericidal action can give a ray of hope among those patients. Prolongation of QT interval is a serious complication of this drug therapy which may happen, although infrequently

KEYWORDS

Drug resistant TB (DRTB), Programmatic management of drug-resistant TB (PMDT), Bedaquiline (Bdq)

INTRODUCTION

Tuberculosis (TB) is a global disease, found in every country in the world. It is the leading infectious cause of death worldwide. The World Health Organization estimates that 1.8 billion people—close to one quarter of the world's population—are infected with Mycobacterium tuberculosis (M.Tb), the bacterium that causes TB. There is growing resistance to available drugs, which means the disease is becoming more deadly and difficult to treat. There were 558,000 cases of drug resistant TB last year. [1]

Emergence of resistance in Mycobacterium tuberculosis against anti-tubercular drugs particularly multidrug-resistant tuberculosis (MDR-TB) has become a significant public health problem in many of the developing countries including India. Under RNTCP, the programme earlier run as DOTS plus has been revised recently and changed to PMDT (Programmatic Management of Drug Resistant Tuberculosis) to make it more user friendly and practical, leaving no scope for development of further resistance and prevent transmission of drug resistant bacilli. Drug-resistant TB (DRTB) is spread the same way that drug-susceptible TB is spread. TB is spread through the air from one person to another. People nearby may breathe in these bacteria and become infected. [2]

Causes Of Drug Resistant TB

Drug-resistant TB can occur when the drugs used to treat TB are misused or mismanaged.

Drug-resistant TB is more common in people who

1. Do not take their TB drugs regularly
2. Do not take all of their TB drugs
3. Develop TB disease again, after being treated for TB disease in the past
4. Come from areas of the world where drug-resistant TB is common
5. Have spent time with someone known to have drug-resistant TB disease

Drug resistant TB commonly arises through the selection of mutant strains due to inadequate chemotherapy. Inadequate previous treatment exert selection pressure and favors the multiplication of resistant tubercle bacilli, which eventually become the dominant population. Bacilli which initially had resistant to only one drug may soon develop resistant to two drugs and then sequentially to many drugs. The primary mechanism of multiple drug resistance in tuberculosis is due to perturbations in the individual drug target genes. The mycobacterial genes involved in drug resistant are Isoniazid-enoyl-acyl carrier protein reductage (inh A), catalage peroxidise (kat-G), Alkyl hydroperoxidereductase (Ahpc), Rifampicin- RNA polymerase subunit B (rpo B). Pyrazinamide- pyrazinamidase(Pnc-A). Streptomycin- Ribosomal protein subunit 12(rpsL),16s ribosomal RNA (rrs).Fluoquinolones- DNA gyrase (gyrA and gyr B).

In addition to these bacterial virulence factors (e.g. W Beijing genotype). host genetic factor may also contribute to drug resistance. The presence of HLA-DRB1 14, DQB1 0503 and DQB1 0502 alleles were found to be significant risk factors for the development of MDR TB.

Types of Drug Resistant TB

Mono-resistant TB (MR TB): A TB patient, whose biological specimen is resistant to one first line anti-TB drug only.

Isoniazid-resistant TB (Hr TB): A TB patient, whose biological specimen is resistance to isoniazid and susceptibility to rifampicin has been confirmed.

Rifampicin resistant TB (RR- TB): A TB patient, whose biological specimen is resistant to R, detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to R, in the form of mono-resistance, poly-resistance, MDR or XDR.

Poly-drug resistant TB (PDR TB) : A TB patient, whose biological

specimen is resistant to more than one first-line anti-TB drug, other than both H and R.

Multidrug-Resistant TB (MDR TB):- Multidrug-resistant TB (MDR TB) is caused by TB bacteria that are resistant to at least isoniazid and rifampin, the two most potent TB drugs.

Extensively Drug-resistant TB (XDR TB):- Extensively drug-resistant TB (XDR TB) is a rare type of MDR TB that is resistant to Isoniazid and Rifampicin, plus any Fluoroquinolone and at least one of three injectable second-line drugs (i.e. Amikacin, Kanamycin, or Capreomycin). Because XDR TB is resistant to the most potent TB drugs, patients are left with treatment options that are much less effective.

XDR TB is of special concern for people with HIV infection or other conditions that can weaken the immune system. These people are more likely to develop TB disease once they are infected, and also have a higher risk of death once they develop TB.

The RNTCP in India

The large scale implementation of the Indian government's Revised National TB Control Program (RNTCP) (sometimes known as RNTCP 1) was started in 1997. The RNTCP was then expanded across India until the entire nation was covered by the RNTCP in March 2006. At this time the RNTCP also became known as RNTCP II.

The initial objectives of the RNTCP in India were:
1. To achieve and maintain a TB treatment success rate of at least 85% among new sputum positive (NSP) patients.
2. To achieve and maintain detection of at least 70% of the estimated new sputum positive people in the community. [3]

PMDT-The programmatic management of drug-resistant TB (PMDT) can be defined as "all associated functions related to providing services based in the TB strategy in order to achieve the targets set for drug-resistant TB in the Global Plan to Stop TB.

Globally, the first WHO endorsed PMDT services began in the year 2000.

History Of PMDT In India

Programmatic Management of Drug Resistant Tuberculosis (PMDT) strategy deals with the prevention and control of MDR-TB through three major components:
(i) High quality DOTS implementation
(ii) Rational use of anti TB drugs
(iii) Strict implementation of infection control measures.

Early detection of MDR-TB suspects and their confirmation by rapid culture testing methods and their uninterrupted and complete treatment is to play key role in prevention of the new MDR cases. Following strategies are being implemented under PMDT.

(a) Good quality DOTS Programme: The existing Directly Observed Treatment of Short course chemotherapy (DOTS) programme launched in 1993 and expanded in 1997 is supported by five components viz. (i) political commitment (ii) diagnosis by quality microscopy (iii) adequate supply of right drugs (iv) directly observed treatment (v) proper reporting and recording.

(b) Case finding of MDR TB suspects: Case finding is the initial link in the process of early diagnosis of MDR TB cases and their prompt treatment which is main objective of the programme.

(c) Referral of M/XDR TB patients: On confirmation of a MDR TB suspect, Medical Officer at Peripheral Health Institute (MO PHI) has to make arrangement of sending two sputum samples (one of which is early morning sample and other one is supervised spot sample) in falcon tubes to RNTCP certified culture and drug sensitivity test laboratory (C-DST lab) along with RNTCP request form having all details of the patient.

(d) Confirmation of the diagnosis (provision of laboratory services): State level designated laboratory termed Intermediate Reference Laboratory or any other designated RNTCP certified C-DST lab should have following facilities: (i) Diagnostic culture on solid and/or liquid media. (ii) Confirmation of resistance to rifampicin by molecular test (Line Probe Assay or any other RNTCP approved technology) (iii) Confirmation of the species as Mycobacterium tuberculosis or non-tubercular Mycobacteria (NTM) (iv) Testing for susceptibility to at least Isoniazid and Rifampicin by solid or liquid culture. Molecular (genotype) tests are much faster than phenotype tests as these don't require growth of organism. The turnaround time for C-DST results by solid LJ media is around 84 days, by liquid culture (MGIT) is around 42 days, by LPA Line Probe Assay) is 72 hours and by CB NAAT (Cartridge Based Nucleic Acid Amplification Test) is around two hours. Diagnosis of MDR TB case is confirmed only when the tests are conducted by RNTCP endorsed testing methods in RNTCP quality assured Culture and DST laboratory.

(e) Treatment of M/XDR-TB cases: A patient on confirmation as MDR TB or XDR TB case is admitted at DR TB centre (Drug Resistant TB Centre) for pre-treatment evaluation and treatment initiation for a minimum period of 7 days or one month respectively. Medicines to all patients of M/XDR TB are provided in the boxes which are to be given under supervision of DOTS provider at DOTS centre.

After successfully establishing RNTCP services across the country in 2006, the PMDT services were introduced in 2007 and complete geographic coverage was achieved by 2013. [4] Definite criteria were set to assess the risk and eligibility for the drug susceptibility test (DST). The DST was thus offered to TB patients who remained smear positive during follow-up; to previously treated patients; those who were HIV positive and people who had contact with a known DR-TB patient. [5] This would then lead to universal DST, i.e., DST to all diagnosed and notified TB patients.

In 2018, the major changes taken place were:-
- Roll out of Shorter MDR Regimen
- Nationwide Bedaquiline access
- Introduction of Delamanid
- Nationwide Delamanid access for 6 to 17 years

In 2019, Revised Guidelines for PMDT in India points towards all oral regimen.

Classes Of Anti -TB Drugs For Treatment Of DR-TB Patients

GROUPS & STEPS		DRUG
Group A: Include all three medicines	Levofloxacin	Lfx
	Moxifloxacin	Mfx
	Bedaquiline	Bdq
	Linezolid	Lzd
Group B: Add one or both medicines	Cloafazimine	Cfz
	Cycloserine OR	Cs
	Terizidone	Trd
Group C: Add to complete the regimen and When medicine from Group A and B cannot be used	Ethambutol	E
	Delamanid	Dlm
	Pyrainamide	Z
	Imipenem-cilastatin OR Meopenem	Ipm-ClnMpm
	Amikacin (OR Steptomycin)	Am (S)
	Ethionamide OR Prothionamide	Eto OR Pto
	p-aminosalicylic acid	PAS

Standard Regimen For MDR/RR TB Or H Mono-poly DR TB:-

Under RNTCP, the following are the standard DR TB regimens:
1. All oral H mono/poly DR TB regime
2. Shorter MDR TB regimen
3. All oral longer MDR TB regimen

Treatment Protocol For DRTB Patients:-

Regimen class	Intensive phase	Continuation phase
H mono/poly DRTB (R resistance not detected and H resistance)		
All oral H mono-poly DR TB regimen@	(6) Lfx REZ	
MDR / RR TB		
Shorter MDR TB regimen@	(4-6) Mfx[h] Km/Am* Eto Cfz ZH[h] E	(5) Mfx[h] Cfz Z E
All oral longer MDR TB regimen@	(18-20) Bdq(6) Lfx Lzd[#] Cfz Cs	

But in our study center, PMDT 2017 guidelines are going on. The duration of Bedaquiline (Bdq) is limited to 24 weeks only and is given according to the following criteria:-

Bedaquiline (Bdq) :-

- A diarylquinoline that specifically targets mycobacterial ATP synthase.
- Strong bactericidal and sterilizing activities against M.tb.
- The drug has an extended half-life, which means that it is still present in the plasma up to 5.5 months post stopping BDQ.
- Week 0–2: Bdq 400 mg (4 tablets of 100 mg) daily (7 days per week) + other drugs;
- Week 3–24: Bdq 200 mg (2 tablets of 100 mg) 3 times per week (with at least 48 hours between doses) for a total dose of 600 mg per week + other drugs; and
- Week 25 (start of month 7) to end of treatment: Continue other second-line anti-TB drugs only as per RNTCP recommendations

Inclusion Criteria For Bedaquiline (Bdq)

- Patient aged > 18 years having MDR/RR TB. .
- Non-pregnant females or females not on hormonal birth control methods are eligible. They should be willing to continue practicing birth control methods throughout the treatment period or have been post-menopausal for past 2 years; and
- Patients with controlled stable arrhythmia can be considered after obtaining cardiac consultation.

Exclusion Criteria For Bedaquiline (Bdq)

- Pregnancy & lactating mother
- Currently having uncontrolled cardiac arrhythmia that requires medication;

Having any of the following QTcF interval characteristics at screening: 1) QTcF ≥ 500 at baseline & normal electrolytes, ECG to be repeated after 6 hours and if both ECGs show QTcF>500 then the patient should not be challenged with cardiotoxic drugs.

2) History of additional risk factors for Torsade de Pointes, e.g. heart failure, hypokalemia, family history of long QT syndrome.

Caution must be exercised that Bdq must not be added to a failing regimen in any MDR/RR TB patients already on DRTB treatment.

Aims & Objectives:

1. To assess the proportion of MDR and XDR TB in patients with drug resistance
2. To determine the incidence of side effects in patients treated with Bedaquiline.

MATERIALS AND METHODS:-

1. **Study Area:-** OPD of Chest Medicine and District Tuberculosis Centre (DTC), Malda Medical College, Malda, West-Bengal

2. **Study Population:-** DRTB patients attending at our study area.

3. **Study Period:-** 8 months (April 2019- November 2019).

Inclusion Criteria:-

a) All patients of both sexes diagnosed as DRTB on the basis of Sputum and CBNAAT reports.

b) All patients of both sexes above 18 years of age taking Bedaquiline containing regimen.

Exclusion Criteria:-

a) Patients not giving consent to participate in the study. b) Patient below 18 years of age.

Sample Size:- 100 patients

Sampling Design:- Consecutive non-probability method

Study Design:- Single centered prospective observational study

Control:- Nil

Method of Data Collection:-

After inclusion into this study, patients were evaluated as mentioned below---

a) Detailed history and clinical examination
b) Baseline investigations and other investigations as found necessary during the study mentioned below

Parameters Of Study:

a) History including duration of illness, history of drug or alcohol use
b) Clinical examination- General Survey and Systemic examination
c) Investigations:-

1. Baseline Investigations:-
a) Blood for Hb%, total leucocyte count, differential leucocyte count, platelet count, ESR, fasting and post prandial glucose, urea, creatinine, liver function test, electrolytes specially serum potassium
b) Electrocardiogram in 12 leads with long lead 2
2. Blood for HIV 1&2 Antibodies, HBsAg, AntiHCV.
3. Sputum for AFB & CBNAAT
4. Sputum for line probe assay (LPA) to 1st & 2nd line drugs
5. Sputum for liquid culture (LC) and drug sensitivity test (DST) to all 1st & 2nd line drugs.
6. 2D Echocardiography

The investigations may be repeated as per requirement based on clinical evaluation

Statistical Analysis Plan:

Descriptive statistics was done by using Mean & Standard Deviation and Frequency Distribution Tables and then inferential statistics was done according to what is needed.

Contribution by the Authors:

Dr Saswata Ghosh, Dr Animesh Mandal,Dr Ajay Agarwalla,Dr Md Naimul Hoque & Dr Monojit Chakraborty,- Concept designing, conducting the study and writing the manuscript.

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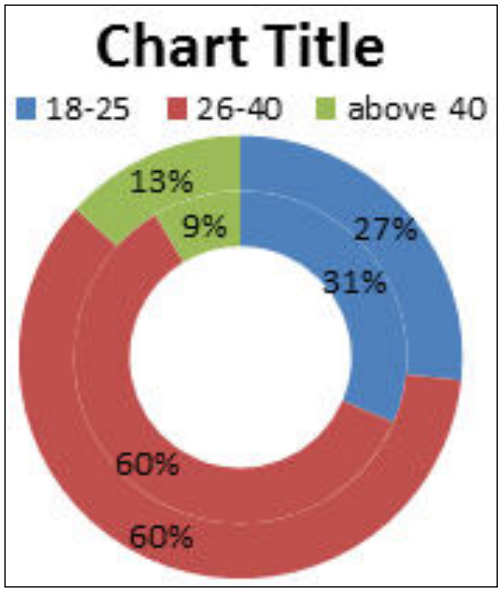
RESULTS

Table-1 Showing Patients On DRTB Regimen In Different Age Groups. Total No Of Patients Were 100.

AGE GROUP	NO OF PATIENTS
18-25	30
26-40	60
>40	10
TOTAL	100

Table-2 Showing Gender Distribution Among All Those100 Patients Who Are On DRTB Regimen



Inner circle- Distribution of male patients
Outer circle- Distribution of female patients

Table-3 Showing Number Of Patients Having Resistance To 1st & 2nd Line ATDs Proved By LPA

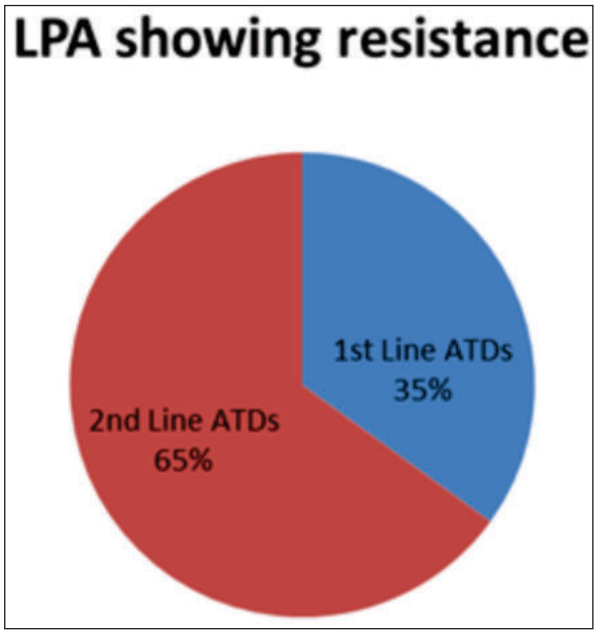


Table-4 Showing Age Wise Distribution Of Patients Getting Bedaquiline (Bdq). Out Of 100 DRTB Patients, 40 Of Them Received Bdq.

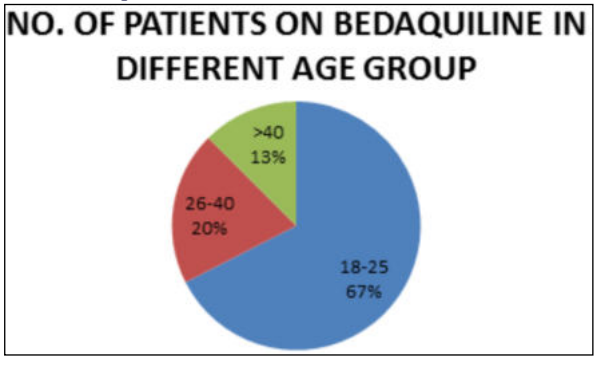


Table-5 Showing 7 Out Of 40 Patients Who Are On Bedaquiline Came Across Some Minor Complications While 33 Of Them Are Completely All Right. (n=5)

Sl no.	Complications	Number	Percentage
1.	Nausea	2	5
2.	Joint pain	2	5
3.	Chest pain	1	2.5
4.	Prolong QT interval	1	2.5
5.	Hypokalemia	1	2.5
6.	No significant complication	33	82.5

DISCUSSION

Large studies on bedaquiline (Bdq) use to treat multidrug resistant (MDR) and extensively drug resistant TB (XDR-TB) are lacking. The information available today on bedaquiline is still limited to phase 2 studies and small individual cohorts treated under clinical trial conditions, the largest study not exceeding 233 patients.

The European Respiratory Journal(ERJ) has recently published several contributions related to the compassionate use of bedaquiline (1,2) and the delamanid , compassionate programmed based on the European Respiratory Society (ERS)/WHO TB consilium(3-9).

In this issue of the ERJ, PYM et al. (10) report result from the TMC207- C209 study. This study was a phase 2, multicentre, open-label, single arm trial (TMC: 207-C209); Clinical Trials, Gov. Identifier; NCT00910871, conduct to confirm the Safety and efficacy of bedaquiline. The trial enrolled 233 patients(63.3% with MDR TB ,18.9% with pre XDR-TB and 16.3% with XDR-TB).

When considering safety, the most common adverse events were those typically observed during Multi Drug Resistant tuberculosis treatment, only six(2.6%) subjects had clinically significant QTcF prolongation (>500ms). Although most frequent drug reaction observed in >10% patients during treatment with bedaquiline in the controlled trial was nausea.

In a retrospective cohort study by Kim CT , Kim T-O ,Shin H-J et al. Published in Eur. J , 2018;51:1702467 found that treatment of patients with MDR-TB with new anti-tuberculosis drugs delamanid and bedaquiline , individually or sequentially ,showed good efficacy and safety in combination with the WHO –recommended background regimens.

Previous clinical trials showed that treatment with bedaquiline for 24wks resulted in sputum culture conversion is 79-81% of patients at 24wk, 62-72% at 120 wks (11, 121, 13). In this study, over all culture conversion rate is >90% at the end of treatment. Although the good efficacy one of the most important safety issue associate with these new anti tuberculosis drugs is , drug induced QTcF prolongation, which is usually asymptomatic and may cause fatal ventricular tachyarrhythmia.

A recent systematic analysis of cardiac safety with bedaquiline treatment involving 1256 patients, including controlled clinical trials and cohort studies, should that QTcF was>500 ms in 3.2% of patients and 0.6 % of patients discontinue treatment due to QTcF prolongation (14)

In another study by Jackie Jones, Vanessa Mudaly et al about the adverse drug reaction(ADR) of the patients of MDR-TB getting bedaquiline in Western Cape Province in South Africa during March '15 to June '16 showed that 35 suspected ARDs were reported in 32 patients, including 13 death.

The ARDs reported to the Western Cape Pharmacovigilance programme are consistent with known safety profile of bedaquiline and other drugs used in MDR-TB treatment. The most common reported ARD in the study was QTcF prolongation (16). Rashes, in particular pastular/ aceneiform rashes were commonly reported.

There was also an unexplained increase risk of death associated with bedaquiline in another study. 10 out of 79 patients randomised to bedaquiline and 2 out of 81 randomised to placebo died. (15, 16)

There is limited data in cardiovascular safety of long term bedaquiline exposure. A South African observational cohort reported minimal increase of QT after bedaquiline initiation , but this study is flawed in that a third of the patients were taking moxifloxacin , which is known to prolong QT, at the time of baseline ECG(17).

CONCLUSION

The aim of our present Study is to retrospectively evaluate the safety and tolerance of bedaquiline(Bdq) containing regime in a observational Cohort of MDR TB patients treated in different area of WB.

In our study out of 100 MDR TB patients (DST proved) ,40 patients has been given bedaquiline along with other anti-tuberculosis drug.

In our study patients (n=40) having Bdq with most common adverse effect is nausea(5%). In a similar Study by PYM et.al (I) nausea occurs in 31.5% patients.

In another study by DIACON et.al (2) complication like nausea is 41%.

In our study other adverse effect like prolong QT interval is only 2.5% similar to other studies (3, 4, 5). In a similar study by PYM et.al QT prolongation is 9.7% and interruption of bedaquiline due to adverse events occur in 5.8% patients. Although information on QT interval in 50% cases and timing of their assessment were not standardised, it seems the majority of cases died for noncardiac cause.

In this study other adverse effects are arthralgia (2.2%), chest pain (2.5%), hypokalaemia (2.5%) and most of the patients (82.5%) have no significant complications. Although another study by PYM et.al arthralgia occurs in 37% cases.

The results of our study demonstrate that overall bedaquiline

containing regimes are relatively safe and has relatively lower occurrence of adverse effects.

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