

PAIN AND SUFFERING IN CANCER PATIENTS

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Abstract: Pain affects most cancer patients due to the disease itself or its treatment and recent studies indicate that persistent severe pain continues to be prevalent despite advances in treatment. The World Health Organization (WHO) ladder and liberal use of opioids still do not provide adequate pain relief in a quarter of patients and pain medicine consultants are often able to help many of them. Unfortunately despite all possible interventions we recognise that a small number of patients still continue to suffer severe uncontrolled pain. In others, whilst the severe physical pain may be controlled, they continue to suffer 'mental and emotional pain' in the form of suffering and loss of autonomy and may undergo existential crises. As such, questions as to the role of medicine, whether to relieve suffering in all its forms or simply to maintain existence without due regard for quality of life are raised.

Keywords: CANCER, DISTRESS, DYING, OPIOIDS, PAIN, SUFFERING

Pain in cancer patients is a difficult and challenging problem to manage for clinicians and healthcare professionals. Most cancer patients experience pain of varying intensity at some point in their cancer journey, and it is prevalent at all stages of the disease, from the time of diagnosis, during treatment and up to their end of life.

The most common reason for pain in patients with cancer is due to metastatic bone disease; tumour invasion of tissues, nerves and other organs can cause severe pain (Davis and Walsh 2004). Treatments like radical surgery, radiotherapy and chemotherapy can also cause damage to tissues and nerves and lead to severe and sometimes chronic pain in these patients.

A third of the pains in cancer patients are considered to be neuropathic

pain due to nerve damage, be it from the cancer or from the treatment of the cancer, but often it is a mixture of neuropathic pain and pain from inflamed organs and tissues (known as nociceptive pain). Patients (and their families) often express a fear of spending the last days of their lives in severe pain and associated suffering.

Studies on Patients' Experience of Cancer Pain

The prevalence of pain in cancer patients has generally been under-recognised until recently. A meta-analysis of 52 studies over a period of nearly 40 years between 1966 and 2005 (van den Beuken-van Everdingen et al. 2007) showed that the prevalence of cancer-related pain is much higher than previously thought. This comprehensive analysis showed that 59% of patients reported poorly-controlled pain during ongoing oncological treatment, and that the experience of moderate to severe pain increased as the disease progressed, with 64–90% of patients with advanced disease in pain towards their end of life. Even in cancer patients who had successful curative treatment, a third of them reported ongoing persistent chronic pain (Pachman et al. 2012). In another review of the published literature of 26 studies, with a total of more than 1500 patients, looking at the treatment of cancer pain (Deandrea et al. 2008) it was found that 43% of patients reported that their pain was undertreated. This could be due to several factors including poor assessment and acknowledgement of pain, lack of medications or reluctance to use them, both by the patients and the clinicians, and treating the pain as a symptom rather than identifying the underlying mechanisms and managing them. The self-reported prevalence of pain in patients attending oncology outpatients was shown to be significant; more than a third of these patients had poor pain control, particularly in their last year of life (Valeberg et al. 2008).

Giant strides have been made in the understanding, surveillance and treatment of cancer over the last two decades, and these have resulted in improved survival rates (and sometimes the cure) of cancers. However, this cannot be said to be true about the successful management of cancer pain.

The WHO pain ladder (World Health Organization 1986) has been widely used as the gold standard in the management of cancer pain. It has been reported that the pain in 90% of patients with cancer pain can be controlled using the step-wise pain ladder (Ventafridda et al. 1985), but six years later it was reported that only 75% of patients with advanced cancer benefitted from the WHO ladder (Grond et al. 1991). Almost twenty years later, one of the largest studies to date on the prevalence, treatment and impact of cancer pain, The European Pain in Cancer (EPIC) Survey, showed that despite the developments, pain in these patients is still poorly controlled and has a significant negative impact on their quality of life (Breivik et al. 2009). This recent study also highlighted that cancer-related pain was widely prevalent, of longer duration and intensity and at times happening with greater frequency than was previously understood. This survey was carried out in twelve European countries where the healthcare systems are well developed, and more than 5,000 patients participated in the study.

In the EPIC Survey (Breivik et al. 2009), 31% of patients reported that pain was the primary complaint that made them decide to visit their doctor and subsequently led to their cancer diagnosis. Almost all patients reported to have pain at some point and more than a quarter of these patients did not have any regular analgesia prescribed, despite being in moderate or severe pain. 57% of patients in the study reported that they had experienced pain every day and 88% of the patients had experienced significant pain during the past month. About 10% (573 patients) of the telephone respondents of the EPIC survey were invited for an in-depth interview about their pain. More than 50% of these patients felt that their quality of life was not considered as part of the clinical management by the healthcare professionals and a third of them felt that their doctor did not have enough time to address their pain issues.

Interestingly, a quarter of the patients felt that their doctor did not know how to control their pain and despite this less than 10% of the patients were referred to specialist pain clinicians or to palliative care teams. Nearly 70% of patients had their pain management supervised by medical oncologists (42%), family practitioners (19%), other specialists (16%) and other health workers (5%). 3% of patients did not have any

clinical input at all into their pain management, despite being in moderate to severe pain. On detailed questioning, two-thirds of these patients reported that their pain was not assessed properly on any validated pain scales and one in four patients could not recall their clinician asking them any questions about their pain. The most poignant observation from this cohort of 573 patients was that despite the existing treatments and input from healthcare professionals, one in three of these cancer patients reported that sometimes the pain is so bad that they felt like they wanted to die.

The findings of all these latter studies contradict the earlier findings of the late twentieth century (Ventafridda et al. 1985) which suggest the WHO pain ladder is able to routinely and reliably control cancer pain. Indeed, other authors have now also questioned the validity and efficacy of the pain ladder (Ferreira et al. 2006, Nolte 2009, Vargas-Schaffer 2010, Zeppetella 2011, Forbes 2011).

Why Are We so Bad at Treating Cancer Pain?

One of the main reasons why the WHO ladder fails to deliver its primary objective of 'Freedom from Cancer Pain' in most patients is the over-reliance on drugs, particularly strong opioids, as the mainstay in the management of pain (Muller-Schwefe et al. 2014). Despite the fact that there has been a better understanding of the limitations of opioids in managing these patients with complex cancer pain (Muller-Schwefe et al. 2014), the practice of giving escalating doses of opioids in an attempt to 'get on top of the pain' and 'make the patient pain-free' is still continued in many practices.

The EPIC Survey also highlighted that opioids are still the most commonly prescribed analgesics for managing cancer pain. 37% of respondents were on weak opioids (Codeine, Dihydrocodeine etc.) and 46% were on strong opioids (Morphine, Oxycodone, Fentanyl etc.). Another finding during the survey was that though most patients initially responded that their pain control with these medications was effective (60%), and very effective (24%), on more elaborate questioning more than two-thirds of these patients acknowledged that the medications

they were currently on were not always adequately controlling their pain (Breivik et al. 2009).

Concerns have been raised over suggestions that the higher doses of opioids required for pain control may contribute towards considering palliative sedation prior to death (Oosten et al. 2011). Even in other groups of patients, there is little evidence for any meaningful improvement in analgesia, and indeed there is evidence for deterioration of quality of life with long-term opioid usage (Munglani 2013) (Munglani 2014).

The Issue of Breakthrough Pain in Cancer

In the EPIC survey, 54% of patients also reported that they experienced breakthrough pain. Breakthrough cancer pain (BTcP) has been defined as a transitory increase in pain intensity on a baseline pain of moderate intensity in patients on analgesic treatment administered at least once a week (Mercadante et al. 2012). Two-thirds of these patients experiencing breakthrough pain did not have any medications prescribed to address this issue.

Nearly half of the patients suffering from cancer-related pain are unaware of the side-effects of their analgesics and adjuvant drugs. This lack of understanding leading to poor compliance with the medications are some of the main reasons pain is not adequately reported and managed in a third of patients suffering from cancer pain (Breivik et al. 2009). Constipation is the commonest reported side-effect followed by nausea & vomiting, sedation and psychological effects. Central nervous system side-effects due to opioid therapy and other analgesics used for managing pain in cancer patients are often under-recognised (Vella-Brincat and Macleod 2007). This can lead on to poor quality of pain control as well as having a significant impact on the quality of life for the patient. Additionally it produces unwarranted strain for the carer and healthcare professionals who are involved with these patients.

Patients who have been diagnosed with advanced cancer also have emotional distress and suffering in addition to the physical pain due to the cancer and the treatment received for it (Mercadante 2014). Distress, or existential suffering, is not always recognised as a separate entity

distinguishable from pain either by patients, relatives or medical staff (Lyness 2004). In assessing pain, when patients are often asked 'are you in any pain?' the answer is almost always in the affirmative, and then they are encouraged to take the prescribed regular or rescue analgesia, usually strong opioids, and often in frequencies as close as every hour. This would invariably lead on to central nervous system side-effects like somnolence, drowsiness and sedation, but also other subtle effects like cognitive dysfunction and memory problems (Vella-Brincat and Macleod 2007). The aforementioned side-effects could be measured using sedation scores and also other early warning scoring systems, but that would identify only a part of the underlying problem. Family members and/or caregivers, who have known these patients for quite some time, often pick up subtle signs like cognitive dysfunction, memory lapses and personality changes. It can be difficult for healthcare professionals to accept that patients with advanced cancer may be addicted to their drugs (Ballantyne 2007) and they would continue to believe that the patients are taking the medications only because they are suffering from their physical pain.

The Lack of Efficacy of Continued Opioids Due to Increased Tolerance and Paradoxical Increases in Pain Perception Due to Opioids (Opioid-Induced Hyperalgesia)

Opioid tolerance (Chang et al. 2007) and opioid-induced hyperalgesia (Silverman 2009) are also often poorly recognised, and giving opioids more frequently and at a higher dose often fuels a vicious cycle, all of which contributes towards poor pain management. Opioid tolerance is a neurophysiological adaptive mechanism that develops in people when they are exposed to opioids for a prolonged period of time, often resulting in requiring higher doses to achieve the same level of analgesia (Chang et al. 2007). It is thought to be due to desensitisation of the anti-nociceptive mechanisms due to prolonged exposure to opioids, and also possibly due to opioid receptor down regulation (Vorobeychik et al. 2008).

Opioid-induced hyperalgesia or opioid-induced abnormal pain sensitivity is a paradoxical increase in pain perception seen in patients who have been using opioids long-term, and is due to sensitisation of pro-nociceptive mechanisms (Gardell et al. 2006). Both opioid tolerance and opioid-induced hyperalgesia would result in dose escalation by the clinically treating staff: this may be useful to improve analgesic efficacy in the opioid tolerant patient (Brinkschmidt and Neumeier 2011), but would be exactly the wrong approach in a subject in a patient with opioid induced hyperalgesia as the further administration of opioid in this situation would paradoxically *increase* the pain sensitivity and lower the pain threshold, thus resulting in overall increased pain experience by the patient (Chang et al. 2007).

Further dose escalations in such patients could result in physical dependence, which is defined as 'a state resulting from chronic use of a drug that has produced tolerance and adverse physical symptoms (withdrawal symptoms) occurring from sudden discontinuation or rapid dose reduction of the said drug' (Meera 2011).

Addiction or substance abuse is the compulsive and repetitive use of a drug (Modesto-Lowe et al. 2012), often at doses that could be harmful and one may develop tolerance and physical dependence as a result of it. Fortunately, addiction is not reported to be common in cancer patients (Ballantyne 2007). However the community wide stigmata associated with addiction leads to an inherent fear amongst patients of taking these medications, and reluctance of clinicians to prescribe them.

Unfortunately and perversely dependence, tolerance and opioid induced hyperalgesia can occur simultaneously in a patient due to the complexities of the pharmacological mechanisms involved and the fact that these opioids may have multiple active metabolites; all of which can have competing effects.

The other consequence of poorly-controlled pain, despite using high doses of strong opioids, is a reliance on other agents like ketamine, benzodiazepines, gabapentinoids etc. resulting in polypharmacy (Kotlinska-Lemieszek et al. 2014). Other modalities used in the management of pain, including cognitive behavioural therapy (CBT), mindfulness and complementary therapy are often not made available to many patients.

The Role of Pain Medicine in Treating Cancer Pain

Interventional management of cancer pain (Bhaskar 2012) is used rarely except in a few specialist centres with trained personnel, despite there being good evidence for it in the management of pain in patients with life-limiting diseases like pancreatic cancer (Bahn and Erdek 2013). Neuroablative (nerve destruction) procedures for intractable pain had been employed for more than 40 years, but their use has declined since better availability of opioids in managing cancer pain, particularly in Europe and North America, along with a major liberalisation in drug policy in the US in the 1970s, the adverse consequences of which are still being felt today (the discussion of which is beyond the scope of this article but see (Hansen 2014) for a critique).

The other reason for moving away from using neuroablative or neurolytic blocks is the higher risk of complications, and this has been replaced by the use of external or implantable intrathecal drug delivery systems (Stearns et al. 2005). The advantage of using intrathecal drug delivery (delivering strong analgesics directly into the spinal fluid) is that equianalgesic doses are only a small fraction (1/300 – 1/1000) of the systemic doses; hence the main central nervous system side-effect profile is very much limited, meanwhile providing excellent analgesia (Upadhyay and Mallick 2012). Unfortunately, not many patients have timely access to these highly specialised pain services.

The WHO ladder has added interventions and intrathecal drug delivery as the fourth step after using strong opioids. However, there is a huge delay in referring patients for suitable interventions. In practice, patients with advanced disease and no potential oncological treatment options, even if only palliative, have to suffer uncontrolled pain and the side-effects due to the systemic opioid therapy (Dale et al. 2011). In the UK, despite NICE Guidelines (Improving Supportive and Palliative Care for Adults with Cancer 2004) that stipulate 'each Cancer Network should have a named specialist for advanced pain management techniques' and 'each Local Specialist MDT should have an anaesthetist with expertise in nerve blocks and neuromodulation techniques' there has been an under-utilisation of these services.

By way of explanation, anaesthetists who have such specialised training and practices in pain became known as Consultants in Pain Medicine and since 2007 have been recognised with their own Faculty of Pain Medicine within the Royal College and can become members after further specialised training and an exam. Many have long since given up their anaesthetic practice and are now running their own independent departments and clinics. Of the authors of this article, one continues to do a limited amount of anaesthesia along with his pain practice (AB) whilst the other has been in full time Pain Medicine for 15 years (RM).

Surveys have shown that in the UK there is patchy provision of services and inconsistent partnership between the specialties of pain medicine and palliative medicine (Linklater et al. 2002). This is confirmed in later studies of 160 UK pain consultants (63% response rate) showing that referral rates from palliative medicine to pain clinics were low, with 53.85% receiving five or less referrals per year (Kay et al. 2007).

Pain Control of Cancer in the UK

The UK is seen as one of the top countries, where cancer pain management and palliative care services are seen as a model to the rest of the world. Cancer Research UK reported that more than 331,000 patients were diagnosed with cancer in 2011 (more than 14 million cases were diagnosed all over the globe in 2012). Going by the above statistics alone, there are at least more than 100,000 patients with poorly-controlled pain, which is of moderate or severe intensity. Most of these patients would be in a situation where their pain is under-reported and under-treated. However with appropriate specialist input and by optimising the pain management with appropriate analgesics, adjuvants and interventions, most of these patients could get adequate and satisfactory pain relief. Despite this, there would be still be a group of patients, albeit small, who are suffering severe pain despite the best efforts of their clinicians and specialists.

A Cancer Patient Experience Survey of more than 67,000 cancer patients carried out by the Department of Health in 2010, answering 74 multiple choice questions, showed that 85% of the patients were satisfied that their doctors did everything they could to control their

pain. Despite this endorsement with positive satisfaction scores, the EPIC survey and other studies have shown that this does not equate to adequate pain-control in a large number of these patients.

Do We Still See Cases of Unbearable Suffering?

As Consultants in Pain Medicine, we are only asked to intervene when other specialties are not managing to control the symptoms of pain, and hence we tend to see pain at the challenging end of the spectrum, i.e. pain uncontrolled by 'conventional' means. In this context, 'conventional' would include those types of analgesics, hypnotics and other medications and infusions which have undoubtedly improved pain control in palliative care settings, including oral and transcutaneous opioids, benzodiazepines, ketamine and topical local anaesthetics.

Despite these major efforts as outlined in the preceding paragraphs, as Consultants in Pain Medicine we still see patients in severe distress; unfortunately they are often over-medicated and confused following quite natural attempts to control their symptoms, and suffer with little or no quality of life.

Fortunately we are able to help some of these patients with optimisation of medication and, on many occasions, often using spinal delivery of the same drugs as mentioned above, or the use of neuroablative techniques. In such situations we never work alone, but in conjunction with our oncology, palliative care and primary care colleagues as well as other specialties as necessary, including surgeons and rehabilitation professionals, and not forgetting volunteers and priests for spiritual support etc.

Unfortunately, at least twice a year, most individual pain consultants come across cases where, despite the interventions of everyone, patients experience pain and distress. They are undoubtedly suffering along with those around them, including family and loved ones and the attending medical and nursing staff. Some of us who are heavily involved with cancer patients in busy tertiary centres see many more cases like that in our practice. In our experience it is in these situations that comments 'to put someone out of their misery' come from patients and their relatives,

or other phrases such as 'I wouldn't let my dog suffer like that' are used to put things into perspective about the suffering. The failure to control the suffering of an individual in such situations diminishes the individual; they are often over-sedated to the point of confusion. Additionally, in our opinion, it undermines the role of the medical and other professionals involved in the care of said patient, who are possibly powerless to act to address the situation.

What the authors want to emphasise, both for ourselves and, it is fair to say, amongst most Pain Consultants in the UK, is that we all predictably see, but thankfully not frequently, cases of patients coming from hospitals, hospices and also in the community, whose pain and distress is not relieved adequately. Indeed it is to be acknowledged that some are suffering terribly for very long periods of time. Fortunately we can help many of them, but there are clearly some we cannot without essentially making the patients heavily sedated. The great difficulty is if there does not seem to be an imminent prospect of dying; this often leads to great distress for all concerned in the decision making.

Our Own Experience

In a previous article, one of the authors (RM), when discussing the concepts of ongoing unrelieved pain and suffering and the pressure to consider euthanasia in such circumstances (Munglani 2012), mentioned a patient with severe rectal pain which defied any response to specialist palliative and pain medicine input. This case was mentioned anonymously to a professional colleague who is opposed to the concept of assisted dying and, whilst discussing what therapeutic options were left, the use of intrathecal phenol was considered. Despite knowing fully that this treatment would have made the patient doubly incontinent and possibly paralyse him permanently, this colleague said to the author that the patient 'should be made to have the treatment even if he did not want to' for achieving better pain control; according to him this was a better option. The latter comment begs the question: Exactly what is the purpose of the medical profession – the simple mere prolongation of existence or, in fact, the maintenance of quality of life? What about

the autonomy of the patient in such a circumstance: to choose what treatment he should have rather than be subjected to?

Reflective Practice to Improve Management of Pain in Cancer

The apparent failure of conventional pain management in cancer should cause us to reflect on our practice and look at all the factors that might be contributing to the persistent experience of pain. We should carefully analyse the situation of the patient and their pain in relation to the diagnosis, and see how it can be improved and ensure that appropriate protocols are being followed. Yet despite adequate resources, some patients continue to be in significant pain, distress and suffering.

Other Symptoms as Well as Loss of Autonomy as a Motivator for Request for Assisted Dying

It is clear that even if one is able to control most symptoms of pain in about 90% of patients with optimal availability of best practice, including protocols, guidelines and drugs/ interventions with the availability of clinicians willing to provide such care (which is not always the case), the simple fact remains some patients continue to request assisted dying, because they have lost the will to live and see only a painful death in front of them.

Their quality of life, in their own eyes, has been so destroyed, particularly with loss of function and bodily image, that they see very little meaning in such continued existence. We have particularly observed this in patients with head and neck cancers and those with pelvic cancers where there is double incontinence and loss of sexual function. We have seen similar views expressed in other non-malignant cases, in cases of severe breathlessness due to chronic obstructive pulmonary disease or heart failure and also motor neurone disease; this has been the experience of many senior clinicians.

The recognition that some patients 'have had enough', despite adequate pain control, is recognised in the literature (Prue et al. 2006,

Fried et al., 2007, Morrow et al., 2002). In particular fatigue, including 'fatigue with life', does seem to be a persistent issue when pain is eventually and thankfully controlled. This has been a topic of discussion elsewhere (Munglani 2012).

Cases of Unrelieved Suffering and Pain in Cancer Despite Significant Medical Input

It must be understood that doctors do not like discussing 'failures of therapy' for a number of reasons. It is not easy for them to accept what is happening despite their best efforts, and this acceptance is even more distressing for the patients and relatives and other caring staff. We have often come across patients, who are clearly suffering, continuing to say to their relatives and attending medical staff that they are 'okay' in order to avoid distressing and upsetting those around them.

Case study 1

The above-mentioned fact was a painful but invaluable lesson learnt by one of the authors (AB) while he started as a Consultant in Pain Medicine at one of the largest cancer hospitals in Europe. Jack (name changed to maintain anonymity) was a senior aircraftman in the RAF when he was diagnosed with Ewing's sarcoma, an aggressive form of bone cancer, for which he underwent an above-knee amputation. He was discharged from the RAF and was working as an electrician when he was diagnosed with a recurrence of his disease, which had by now spread to his left lung and chest-wall. He was first seen in the pain clinic for advice regarding the management of his phantom limb pain and stump pain. This was addressed successfully and he carried on with his chemotherapy and radiotherapy.

It was evident that the disease was progressing at a rapid rate and this resulted in severe chest wall pain despite adequate medical management. He had excellent analgesia following a selective nerve destructive procedure targeting the chest wall; a few weeks later this was repeated to target the base of the lung and the diaphragm. The pain from his chest wall was very well controlled, but he was keen on

reducing his opioids as it was now making him very drowsy following the pain interventional procedures. Jack was aware that he was dying and wanted to have 'a Christmas that everyone will remember'. We decided to deliver his opioids via an intrathecal catheter and he was transferred to the hospice for continuing care. Jack's family and friends organised a large barbecue party, which was attended by more than a hundred friends and family members.

Despite very good pain control, Jack was distressed as he was getting increasingly breathless due to the tumour filling his chest cavity, and this was also made worse by panic attacks, especially at night affecting his sleep. Increasing lymphedema, with the fluid retention affecting both lower limbs, further compounded this and this restricted his wheelchair mobility significantly. Jack felt that he should rather die than suffer like this, but efforts were being made to keep him settled with multiple combinations of medications, which made him very drowsy and confused. In moments of lucidity he made it clear that he wanted to die, as he did not want to suffer anymore. This continued for a fortnight, despite being on a 'care of the dying' pathway and on most days Jack reiterated to all concerned that he just wanted to die. One evening Jack said his goodbyes to his family and to his medical team, including the author (AB), and said he wished he would not wake up the following day. And he didn't.

Case study 2

On reflection, this is in stark contrast to what has happened to another serviceman in recent memory. Senior Aircraftman Mike Goody of the RAF brought pride to our nation by winning four gold medals in the recently concluded Invictus Games 2014. Mr. Goody was on patrol in Afghanistan in 2008 when he was trapped beneath his vehicle for more than three hours after it ran over an IED. This resulted in a compound fracture of his left ankle, which required multiple surgeries over the next two and a half years. During this time he suffered depression, nightmares, alcoholism and Post-traumatic Stress Disorder (PTSD). The doctors advised him to have further surgeries to improve the situation, but he was suffering ongoing intractable pain, which made him frustrated as he felt he was depending on his friends and family to move around. He convinced his

doctors to perform a below knee amputation and the rest is history – winning four gold medals in the Invictus Games; he is now training to be a paramedic.

This raises the ethical dilemma of how one patient can have his normal but painful limb amputated when it was saved from severe trauma, but yet another, who was dying from a terminal illness, was allowed to continue to suffer needlessly despite all efforts from the treating team? In our minds, we did not achieve anything by prolonging Jack's life against his wishes; we just prolonged his suffering and the inevitable death for weeks.

Conclusion

The management of symptoms and the distress experienced by patients facing death are sometimes beyond the realms of medicine. Doctors and other healthcare professionals find themselves helpless in these situations, where they are failing in their duty of care despite their best efforts. Involvement of pain and palliative care specialists, and with spiritual and family support, we may be able to alleviate the suffering of most of these patients. We need to accept that sometimes we cannot cure certain diseases and alleviate certain symptoms. Then the efforts should be towards respecting the wishes of the patient whilst maintaining their dignity and also their independence of body, mind and spirit. The lawmakers of the land should support these patients and their clinicians at looking to support not only the right to live, but also the right to die without enduring unnecessary suffering.

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