1. INTRODUCTION

Breakthrough pain in cancer patients (BTP) is defined as a temporarily deterioration of pain that occurs spontaneously (27%) or can be activated (43%) by movements, laughing, sneezing, coughing, hollow organs distension and psychosocial stimuli, where the main pain is stable and under control.

BTP is usually connected with bone pain (27%), tumor invasion of the soft tissue (21%) and brachial plexus syndrome (9%) (1-3). In 17-30% of cases BTP is related to inadequate analgesic treatment, analgetics sub-dosing or too long interval between doses, which leads to so-called ‘Pain at the end of dose’. The breakthrough pain in cancer patients can be caused due to the damage of nerve by cancer or anticancer therapy and BTP can be classified as noioceptive, visceral or neuropathic (4). BTP prevalence is estimated on 50-70% among patients undergoing active oncological treatment, and 70-95% in patients with advanced cancer diseases (5-6). In 92% of patients BTP is described as severe and intense pain (7-10 per NRS) with fast, paroxysmal beginning (less than 3 min) and average time in achieving ‘peak pain’ for less than 10 minutes. In 80-90% of cases it lasts from 1 min to 1 hour (typically between 15 and 30 min), and the average frequency in patients in advanced stages of cancer disease is 4-7 pain episodes daily (7-8). Inadequately controlled BTP causes reduction of confidence in medical treatment efficacy and leads to sleep disorders, anxiety, depression, sense of isolation, fear and sometimes the decision on the rejection of further treatment efficacy and leads to sleep disorders, anxiety, depression, sense of isolation, fear and sometimes the decision on the rejection of further treatment efficacy and leads to sleep disorders, anxiety, depression, sense of isolation, fear and sometimes the decision on the rejection of further treatment efficacy and leads to sleep disorders, anxiety, depression, sense of isolation, fear and sometimes the decision on the rejection of further
medical treatment compromising the quality of life of patients (9-10). Any increase in the pain intensity or appearance of pain before regular opiate dose, needs to be carefully considered, following the possible causes of BTcP, such as its characteristics (11). The breakthrough pain treatment involves the usage of additional so-called ‘Rescue doses’ which should be recorded and included in the following day in adjusted doses of regular analgesic therapy. In most cases, BTcP can be successfully controlled by combination of pharmacological and non-pharmacological therapeutic measures (12). Oral opioid preparations of short-acting are recommended as first-line BTcP treatment because they are easy to use, they act relatively fast and most physicians have a lot of experience in their usage (13). The main deficiency of BTcP oral treatment is the slow onset of action (20-30 min) with maximum effect only after 45-60 min (14). The sublingual drug application would undoubtedly speed up the effect of a medicin, but morphine, because of its hydropobicity, absorbs through the mucuos membrane and the effect of sublingual application is then not faster than oral (15). The much faster onset of activity is achieved by using a type of oral transmucosal composition of fentanyl citrate, which is 80 % of the non-ionized form, absorbed through mucus membrane, in 3-5 min passes through the blood brain barrier, with the peak effects of 20-40 min and the total duration of 2-3 hours after the use (16-19). Better effects in the BTcP treatment are achieved using fentanyl in the form of: 1) sublingual tablets (SLF) (20); 2) intranasal fentanyl spray (INFS) (21-22) and 3) fentanyl buccal soluble film(FBSF) (18).

The aim of this research was to follow characteristics of breakthrough pain (BTcP) caused by a cancer and other most common symptoms (ESAS) at patients in advanced stage of cancer disease, in palliative care.

2. PATIENTS AND METHODS

Prospective study included 433 patients treated in Palliative Care Centre, UKC Tuzla, Bosnia and Herzegovina. General condition of patients was assessed Karnofski score during admission and after 10 days of treatment and dominant following symptoms by ESAS scale daily for 10 days. Group 1 included the patients (353) whose basal cancer pain was of 4-7 intensity per NRS treated by weak opiates (basal analgetic - fixed combination of tramadol/paracetamol (37.5 mg/325 mg) in the initial dose of 3x tbl for pain intensity 4, up to 2x tbl for pain intensity 7). In group 2 (80 patients) basal pain of intensity 8-10 was treated strong opiates as basal analgetic (oral morphine preparation and transdermal fentanyl). Dialy (10 days) breakthrough pain was evidenced and if previous day existed 2 or more breakthrough pain that demanded “rescue dose” of analgetics (tramadol 50-100 mg per os in group 1 i.e. oral morphine 8-12 mg in group 2), basal analgetics dose was increased.

The study didn’t include patients that were allergic to opiates or if they had uncontrolled vomiting or interfered with the oral analgetics application. This study can conducted in accordance with declaration from Helsinki. Statistical analysis was conducted using biomedical application software called MedCalc for Windows version 9.4.2.0. For testing the repeated measurement of paired samples, depending on the distribution of variables, paired T-test and Wilcoxon tests were used.

3. RESULTS

The research was conducted by 433 patients, average age 60.08 ± 10.15 age (from 24 to 87 years), of which 261 (60.28%) male and 172 (39.72%) female patients. 142 (32.79%) had verified metastatic changes in bones, while at 291 (67.21%) patients didn’t have bone metastasis (p<0.0001)(Table 1). Among patients 33.1% were the patients with lung tumor; 21.1% were with digestive tract patients, 15.6% were patients with ORL tumor, 15.1 % were breast tumor patients while patients with other tumors were less than 10% (Table 2). Mean value for Karnofski score for all 433 patients during the reception was 46.63 ± 10.46 and during the release of patients was 54.11 ± 11.7 which is statistically significantly better (p<0.0001). There was no statistically significant difference between mean values for Karnofski score between patients of group 1 and group 2 neither the first day of treatment (p=0.64), nor the tenth day of treatment (p=0.946).

### Characteristics of breakthrough pain (BTcP)

The total number of recorded breakthrough pain in all 433 patients for 10 days was 3 369 (0.78 BTcP/patient/dialy), where at group 1 patients (treated by weak opiates) were recorded statistically less (p<0.0001; 0.56 BTcP/patient/day) when compared with group 2 patients (treated by strong opiates) with recorded 1.75 BTcP/patient/day. In group of patients treated by strong opiates (group 2), during first three days of treatment, 578 (4.4%) BTcP or 2.41/BTcP/pat/day were registered.

| Groups | Group 1** | Group 2*** |
|--------|-----------|------------|
| Number of patients (433) | 353 | 80 |
| Age | 58.75 ± 10.02 | 62.11 ± 9.61 |
| Gender | | |
| M (%) | 211 (48.73) | 50 (11.55) |
| F (%) | 142 (32.79) | 30 (6.93) |

### Table 1. General and demographic characteristics of patients *Mean value Patients treated **weak opiates; ***strong opiates

| Subgroups | Bone metastasis | Bone metastasis |
|-----------|-----------------|-----------------|
| Yes | No | No |

### Table 2. Cancer localization (topographic and clinical) and bone metastasis
which is statistically remarkably more when compared to group 1, in which in the same interval period registered 637 BTcP (32.29%) or 0.60 BTcP/pat/day. In the following two interval periods there were no statistically significant difference in BTcP number in group 1 and group 2 patients (Chart 1). 1 408 (41.79%) BTcP were recored at 142 patients with verified bone metastasis or 0.992 BTcP/patient/day, while at 291 patients without verified bone metastasis 1 961 BTcP or 0.676 BTcP/patient/day were recorded which is statistically remarkably less (p<0.0001). The average intensity of BTcP was 5.91, where in group 1 was 4.51 and 8.04 in group 2. Out of totally registered 3 369 breakthrough pain, 582 (17.28%) were graded by 7, of which 539 (92.61%) were successfully couple by strong opiates and 43 (7.39 %) by weak opiates. It is similar for 556 (16.5%) BTcP which were graded by grade 8, of which 540 (97.12%) were coupled by strong opiates and only 16 (2.88%) were successfully coupled by weak opiates (Chart 2). Of totally 1973 registered BTcP at group 1 patients (treated by weak opiates), the most of them were graded by grade 5 (753 or 38.17%), and then by grade 4 (741 BTcP or 37.56 %). Significantly less BTcP(263 or 13.3 %) is graded by grade 3, then by grade 6 (157 or 7.96 %), grade 7 (43 or 2.18%) and the least grade it by grade 8 (16 or 0.81%). There were no BTcP graded by 1, 2, 9 and 10 (Chart 2). At group 2 patients (treated by strong opiates), of totally 1396 registered BTcP, 540 or 38.68 % were graded by 8. 539 or 38.61 % by grade 7. Significantly less (p<0.0001) BTcP is graded by 9 (253 or 18.12%) and grade 10 (64 or 4.58%). There were no BTcP graded by 1 or 6 (Chart 2).

**Time of occurrence of breakthrough pain (BTcP)**

Analysing the time of occurrence of BTcP at all 433 patients, it has been found that 1967 (58.39%) breakthrough pain came up in evening and night hours (from 18 – 06 hours) and that it is statistically remarkably more (p<0.0001) regarding the 1402 (41.61%) BTcP that are registered in daily hours (from 06 – 18 hours). The most, 1 116 (33.13 %) of BTcP is recorded in time from 18 to 24 hour, and comparing it with other time periods, we can see that in period of 24 to 06 hours is recorded 851 (25.26 %) BTcP; in period od 12 to 18 hours 870 (25.82 %) BTcP (p<0.0001), and the least breakthrough pain (532 or 15.79 %) in period between 06 to 12 hours (p<0.0001). (Chart 3). Analyzing the biggest number of breakthrough pain according to groups is registered in time from 18 to 24 hours (716 in group 1 and 410 in group 2), and the least in time between 06 to 12 hours (246 in group 1 and little more in group 2, that is 286)(Chart 3). Out of totally 3369 breakthrough pain registered at all 433 patients, the most of BTcP (1290 or 38.29%) lasted less than 10 minutes, 882 (26.18%) between 16 and 20 minutes, 752 (22.32%) between 11 and 15 minutes (p<0.0002), 407 or 12.08% between 21 and 30 minutes (p<0.0001) and 38 (1.13%) lasted longer than 30 minutes (Chart 4).

In group 1 statistically more BTcP lasted less than 10 minutes (820 or 41.56%) when compared to 470 or 33.67 % in group 2 (p<0.0001). At the same time there is significantly more BTcP in period between 11 and 15 minutes at patients in group 1 (617 or 31.27%) comparing to group 2 (135 or 9.67%) (Chart 4). Conversely to that, in group 2 most of BTcP lasted between 16 and 20 minutes [(534 or 38.25%), while the same duration was recorded at 348 (17.64%) BTcP in group 1, which is statistically less (p<0.0001), and between 21 and 30 minutes [(250 or 17.91%) in group 2 compared to 157 or 7.96 % in group 1 (p<0.0001)](Chart 4).

**Impact of pain and pain treatment by opiates on accompanying symptoms by ESAS scale**

For most common symptoms in advanced stage of cancer disease (following the Edmonton scale for grading symptoms) in all 433 patients of both groups, the average score, calculated at the first day of reception of patients was 4.48±0.89 (40.31±8.08 as sum of average values of all symptoms), and after 10 days of treatment 3.01±0.82 (27.09±7.38), which is statistically better result comparing to reception day. Average value of pain for all 433 patients for the first day of treatment was 6.09±1.39 which is statistically remarkably more (p<0.0001) regarding the average pain intensity on the tenth day of
treatment (1.64±0.68). In group 2 patients pain intensity was remarkably larger during first 6 days of treatment comparing to group 1 patients, from 7-th to 9-th day there were no significantly remarkable difference, while the pain intensity was significantly smaller at 10th day of treatment (p<0.0001) at patients who were treated with strong opiates (Chart 5). The average values of dispnea at all patients at the first day of treatment was 4.39±1.86 and at the tenth day it was 3.10±1.63 (p<0.0001). Vomiting intensity at the reception was 0.58±0.98 and tenth day of treatment it was 0.44±0.72, and there were no statistically significantly remarkable difference (p=0.015), while the average value for fatigue at the reception was 5.11±1.52, and tenth day it was 3.82±1.48 (p<0.0001).

The appetite at the tenth day of treatment was considerably better (4.03±1.55 v 5.26±1.61 first day; p<0.0001) (Chart 6). Sleepiness was considerably less expressed at the tenth day of treatment (2.86±1.42)(p<0.0001) comparing to the first day of treatment (3.61±1.34). The average value of anxiety during the first day of treatment was 5.06±1.52 and tenth day it was 3.75±1.45 (statistically considerably less p< 0.0001), while the average value for depression was statistically considerably less at the tenth day (3.59±1.39) comparing the first day of treatment (4.75±1.45) (p<0.0001). At the reception, the average of estimated general condition was 5.45±1.45 which is statistically remarkably worse grade (p<0.0001) compared to average result at the tenth day (p<0.0001) (Chart 6).

4. DISCUSSION

By symptom treatment, average value for Karnofski score in our study has improved from 46.63±10.46 at the reception to 54.11±11.7 at the release. In a study that has been following up the effects of treatment of cancer pain by strong opiates (transdermal fentanyl), Karnofski score was relatively constant during the treatment, with average value of 69±2 at the first day and 68±2 at the end of second month (23). The study od Marinangelio and its cooperates (2004) at 48 patients with advanced cancer has showed, contrary to our study, that after the pain treatment with opiates despite the considerably reduction of pain intensity (p=0.04), comes to statistically considerable reduction of Karnofski perfomance status (from 58.92 ± 5.56 at the reception, with the reduction of -24.04) and measure of quality of life which supports the worsening of general condition (24).

In our study, at patients whose elementary pain was treated by strong opiates (group 2) 1.75 BTcP/patient/day was registered, with average intensity of 8.04 (NRS), which is considerably larger the number and the intensity BTcP when compared to group 1 patients (elementary pain treated by weak opiates) [(0.56 BTcP/patient/day of average intensity of 4.51 (NRS)]. From 582 (17.28%) BTcP which were graded by grade 7, 539 (92.61%) were coupled by strong opiates and 43 (7.39%) by weak opiates. Similarly, from 556 (16.5%) BTcP which were graded by grade 8, 540 (97.12%) were coupled by strong opiates and only 16 (2.88%) were successfully coupled by weak opiates. Most of BTcP in group 1 were graded by grade 5 (753 or 38.17%) or 4 (741 BTcP or 37.56%) and in group 2 by grade 8 (540 or 38.68 %) or grade 7 (539 or 38.61%).

The study has been done on patients treated in palliative care, in which fast-acting oral morphine for breakthrough pain control was used, states the average number of breakthrough pain of 2.9 (1-5.5) by patient per day, with average intensity BTcP of grade 7 (by NRS) (25). Korean study from 2016, done on 609 patients, states that the frequency of BTcP is 29.1% (177), where the mean value and median BTcP were 1.95 and 2. The duration of BTcP at 110 patients was up to 10 minutes, at 29 patients it was between 11 to 20 minutes, at 5 patients between 21 to 30 minutes, at 3 patients between 31 and 60 minutes and at 6 patients longer than 60 minutes (26).

Zeppetelle and co. (2000) state that the average frequency of breakthrough pain was graded 4 daily (between 1 and 14), where the BTcP in the 16 % of cases was evaluated as mild (1-3 per NRS), in 46 % as medium strong (grades 4,5,6), in 36% as strong (grades 7,8 and 9) and in 2% as nondurable (grade 10) BTcP, with average duration of 35 minutes (span between 15 and 60) (27). Davies and co. (2008) (11) while exploring 120 patients older than 18 years in different stage of malignancies, at 87 patients (72.5%) registered BTcP with the average frequency of 2 breakthrough pain daily (span between 1 and 10), with average duration of breakthrough pain episodes of 10 minutes (between 5 seconds and 360 minutes), with intensity BTcP to 4 per NRS at 10 patients, to 6 at 45 patients and between 7 and 10 at 31 patients.

The research conducted in Poland, with survey done by 135 doctors that treat the patients in palliative stage of disease, shows that 98.32% of doctors diagnosed breakthrough pain, whose frequency was between 2 (43% of doctors) and 4 episodes daily (7.41% doctors). The most common duration of breakthrough pain was 15 to 30 minutes (27.4%), then up to 5 minutes (23%) and between 5 to 15 minutes (17.8%), until three doctors didn’t plead about duration of breakthrough pain. In pain therapy patients usually used morphy (96.3%), fentanyl
(78%), NSAIL (73%), tramadol (66%) and acetaminofen (61%) (28). Out of totally 3369 breakthrough pain registered at our patients (433), 1967 or 58.39% were registered in night hours (from 18 to 06 hours), of which 1116 (33.13%) were registered in period of 18 to 24 hours and 851 (25.26%) between to 24 to 06 hours. Between 12 and 18 hours 870 (25.82%) BTcP were registered, and the least of them (532 or 15.79%) between 06 and hours. Fine and Busch’s study states opposite results in which 86% patients felt increased pain intensity and bigger BTcP during day, while only 45% patients felt pain during the night (25) Similary, the Bruere and co. Study states that 45 out of 61 patients (76%) have received most of its additional „rescue” doses od narcots for BTcP between 10 and 22 hours, which shows that at these patients the larger breakthrough pain number (from total average of 2.17 BTcP/patient/day) is registered in that period (29). In our study 1408 (41.79%) BTcP is registered at 142 patients with verified bone metastasis or 0.992 BTcP/patient/day, while at 291 patients without verified bone metastasis or 0.674 BTcP/patient/day, which is statistically considerably less (p<0.0001). Also, the Radbruch and co. studies agree that bone metastasis are the cause of enlargement of intensity breakthrough pain, which is harder to control (30, 31).

5. CONCLUSION

The most of this research was aimed at breakthrough pain (BTcP) which occur during the treatment between middle to strong basal cancer pain (6-10 per NRS) by the strong opiates, although we were during our study recorded relatively large number of breakthrough pain of smaller intensity (3-6) at patients treated with weak opiates, and which are also adversely impacted at the satisfaction od patients by pain treatment and demanded additional doses of analgetics. In a smaller percentage it is possible to treat breakthrough pain of stronger intensity (7 and 8) with maximum doses of weak opiates (in case that patients rejects to take strong opiates, opiofobies etc) although there is a better effect when introducing strong opiates as rescue doses. Bone pain caused by metastasis in advanced stage of cancer disease is the cause of larger number of breakthrough pain of bigger intensity with the need of introducing adiotionel therapy next to opioid preparates. The most breakthrough pains were registered in period between 18 and 24 hours, although the cause is not completely clear.

REFERENCES

1. Davies AN, Dickman A, Reid C, Stevens AM, Zeppetella G; Science Committee of the Association for Palliative Medicine of Great Britain and Ireland. The management of cancer-related breakthrough pain: recommendations of a task group of the Science Committee of the Association for Palliative Medicine of Great Britain and Ireland. Eur J Pain. 2009; 13:331-8.
2. Svendsen K, Andersen S, Arnason S, Arner S, Breivik H, Heiskenen T, Kalso E, Kongsgaard U, Sjøgren P, Strang P. Breakthrough pain in malignant and non-malignant diseases: a review of prevalence, characteristics and mechanisms. European Journal of Pain. 2005; 9(2): 195-206.
3. Wincent A, Liden Y, Arner S. Pain questionnaires in the analysis of long lasting (chronic) pain conditions. Eur J Pain. 2003; 7(4): 311-21.
4. Portenoy RK, Hagen NA, Breakthrough pain: definition, prevalence and characteristics, Pain, 1990; 41: 273-81.
5. Payne R. Recognition and diagnosis of breakthrough pain. Pain Med. 2007; 8(1): 51-2.
6. Caraceni A, Martini C, Zecca E, et al., Breakthrough pain characteristics and syndromes in patients with cancer pain. An international survey, Palliat Med. 2004; 18: 177-83.
7. Hwang SS, Chang YT, Kasimis B. Cancer breakthrough pain characteristics and responses to treatment at a VA medical center. Pain. 2003; 101(2): 55-64.
8. Breivik H, Cherny N, Collett B, et al., Cancer-related pain: a pan-European survey of prevalence, treatment, and patient attitudes, Ann Oncol. 2009; 20: 1420-33.
9. Fortner BV, Okon TA, Portenoy RK, A survey of pain-related hospitalizations, emergency department visits, and physician office visits reported by cancer patients with and without history of breakthrough pain, J Pain. 2002; 3: 38-44.
10. Kirsh KL, Whitecomb LA, Donaghy K, et al., Abuse and addiction issues in medically ill patients with pain: attempts at clarification of terms and empirical study, Clin J Pain. 2002; 18: 552-60.
11. Davies AN, Dickman A, Reid C, et al., Breakthrough cancer pain, BMJ. 2008; 337: a2649.
12. Zeppetella G, Breakthrough pain should be distinguished from background pain, Guidelines in Practice. 2009; 12(3).
13. Schug SA, Chandrasena C. Pain management of the cancer patient. Expert Opin Pharmacother. 2015; 16: 5-15.
14. Bailey F, Arora A. Oral opioid drugs. In: Davies A. (ed.) Cancer-related breakthrough pain. Oxford: Oxford University Press.2006: 43-55.
15. Davis T, Miser AW, Loprinzi CL, et al., Comparative morphine pharmacokinetics following sublingual, intramuscular, and oral administration in patients with cancer. The Hospice Journal. 1993; 9: 85-90.
16. Mystakidou K, Katsoouda E, Parpa E, Tsiafas ML, Vlahos L. Oral transmucosal fentanyl citrate for the treatment of breakthrough pain in cancer patients: An overview of its pharmacological and clinical characteristics. American Journal of Hospice and Palliative Medicine. 2005; (223): 228-32.
17. Zeppetella G, Davies AN. Opioids for the management of breakthrough pain in cancer patients. Cochrane Database Syst Rev. 2013; 10: CD004311.
18. Mercadante S. Pharmacotherapy for breakthrough cancer pain. Drugs. 2012; 72: 181-90.
19. Davis MP. Fentanyl for breakthrough pain: a systematic review. Expert Rev Neurother. 2011; 11: 1197-216.
20. Chiewked C, McKeage K. Fentanyl sublingual in breakthrough pain in opioid-tolerant adults with cancer. Drugs. 2010; 70: 2281-8.
21. Kress HG, Ororiska A, Kazmarch Z, et al. Efficacy and tolerability of in-transal spray 50 to 200 mg for breakthrough pain in patients with cancer: a phase III, multinational, randomized, double-blind, placebo-controlled, crossover trial with a 10-month, open-label extension treatment period. Clin Ther. 2009; 31: 1177-91.
22. Radbruch L, Torres LM, Ellershaw JE, et al. Long-term tolerability, efficacy and acceptability of fentanyl pectin nasal spray for breakthrough cancer pain. Support Care Cancer. 2012; 20(5): 565-72.
23. Sloan F, Moulin DE and Hays. A Clinical Evaluation of Transdermal Therapeutic System Fentanyl for the Treatment of Cancer Pain. Journal of Pain and Symptom Management. 1998; 16(2): 103-11.
24. Marinangeli F, Ciccozzi A, Leonardis M, Aloisi L, Mazzei A, Paladini A, Porzio G, Marchetti P, Varrassi G. Use of Strong Opioids in Advanced Cancer Pain: A Randomized Trial. Journal of Pain and Symptom Management. 2004; 27(5): 409-16.
25. Fine PG, Busch MA. Characterization of Breakthrough Pain by Hospice Patients and Their Caregivers. Journal of Pain and Symptom Management. 1998; 16(3): 179-83.
26. Baek SK, Kim do Y, Kang SY, Sym SJ, Kim YS, Lee JY. A Korean nationwide survey of prevalence, treatment, and patient attitudes, Ann Oncol. 2009; 20: 1420-33.
27. Zeppetella G, O’Doherty CA, Collins S. Prevalence and characteristics of breakthrough pain in cancer patients admitted to a hospice. J Pain Symptom Manage. 2000; 20(2): 87-92.
28. Janecki M, Janecka J, Pyszkowska J. Diagnosis and treatment of cancer breakthrough pain in opinions of physicians working in Outpatients’ Palliative Care Units and Pain Clinics. Advances in Palliative Medicine. 2012; 11: 43-7.
29. Bruera E, Macmillan K, Kuehn N, Miller MJ. Circadian distribution of the need of introducing additional therapy next to opioid preparates. The most breakthrough pains were registered in period between 18 and 24 hours, although the cause is not completely clear.

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