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## **The impact of tramadol and dihydrocodeine treatment on quality of life of patients with cancer pain**

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**The impact of tramadol and dihydrocodeine treatment on quality of life of patients with cancer pain**

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3 **The impact of tramadol and dihydrocodeine treatment on**  
4 **quality of life of patients with cancer pain**  
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35 Running head:  
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38 Tramadol and dihydrocodeine impact on QL of cancer pain patients  
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## Abstract

**Background:** Tramadol and dihydrocodeine (DHC) are analgesics of step 2 WHO analgesic ladder (opioids for mild to moderate pain, weak opioids) frequently used in the treatment of cancer pain of moderate intensity. The aim of the study was to assess the impact of tramadol and DHC treatment on quality of life (QL) and performance status (PS) of patients with cancer pain.

**Patients and methods:** Randomized, cross-over, clinical study of 40 opioid-naive patients with nociceptive cancer pain who received tramadol or DHC controlled release tablets for 7 days, then drugs switched and administered for another 7 days. Pain was assessed by VAS (visual analogue scale), QL by EORTC QLQ C 30; PS by ECOG and Karnofsky.

**Results:** From 40 patients recruited thirty completed the study. DHC treatment provided better analgesia (VAS). In QL functional scales better emotional functioning in tramadol group; better global QL and cognitive functioning in DHC group were observed. In symptom scales less fatigue, pain and sleep disturbances, less nausea and vomiting and better appetite in DHC group were noted. In tramadol group less constipation and less financial problems were observed. No differences in dyspnoea and diarrhoea were noted. ECOG and Karnofsky PS were low and did not differ between tramadol and DHC groups.

**Conclusions:** DHC treatment was associated with better global QL, cognitive functioning, analgesia and appetite, less fatigue, sleep disturbances, nausea and vomiting. Tramadol therapy was connected with better emotional functioning, less constipation and financial problems. PS deteriorated in both tramadol and DHC groups.

**Key words:** cancer pain, dihydrocodeine, performance status, quality of life, tramadol

### What is already known on this topic?

Tramadol and dihydrocodeine are weak opioids used in the treatment of chronic and cancer pain of moderate intensity. Analgesic efficacy and adverse effects of both opioids were assessed in a number of clinical trials and in experimental studies. However equianalgesic doses of the drugs were not clearly established in clinical trials. The most common adverse effects of tramadol is nausea, sweating and dizziness and of dihydrocodeine constipation, nausea and sedation.

### What does this article add?

No studies in patients with cancer pain directly compared the drugs. This is the first clinical study that addresses analgesia, adverse effects and quality of life in patients with cancer pain treated with tramadol and dihydrocodeine in a cross-over design. Equianalgesic doses of tramadol and dihydrocodeine were established, the most common adverse effects of the analgesics identified and the guidelines of prophylaxis of tramadol and dihydrocodeine adverse effects were discussed

## Introduction

Tramadol and dihydrocodeine (DHC) are analgesics of step 2 of the WHO analgesic ladder (opioids for mild to moderate pain, weak opioids), which are still frequently used in the treatment of cancer pain of moderate intensity. A number of studies indicate usefulness of weak opioids especially tramadol [1-3] and DHC [4-8]. A significant percentage of patients with cancer and chronic non malignant pain of moderate intensity may benefit from these drugs. However weak opioids are often neglected as a consequence of high efficacy of opioids for moderate to severe pain (opioids of step 3 WHO analgesic ladder, strong opioids) supported by clinical studies [9–12]. These studies are not quite convincing because of limited number of patients recruited. It seems also appropriate to administer weak opioids in moderate pain and strong opioids in patients with severe pain intensity. Studies comparing analgesia and adverse effects of high tramadol with low morphine doses indicate better global QL [13] and less adverse effects during tramadol treatment with similar analgesia [14,15]. Analgesic effect of weak opioids may be also improved by concomitant administration of NSAIDs, metamizole or paracetamol with tramadol, codeine or DHC [16].

Tramadol is an opioid agonist, which apart from opioid action activates pain inhibitory system (increase of noradrenaline and serotonin level). In comparison to other opioids (morphine, pethidine, buprenorphine) tramadol displays small affinity to mu opioid receptors, rarely causes respiratory and circulatory depression and physical dependence [1]. Tramadol in the dose 100 mg causes similar analgesia to 10 mg of morphine when the drugs are given orally [2]. The active metabolite O-desmethyltramadol possesses significant mu opioid receptor affinity and displays analgesic activity [3]. Tramadol is available in immediate and controlled release (CR) oral formulations.

Dihydrocodeine (DHC) is a semi synthetic codeine derivative, which was formed by the hydrogenation of the double tie in the main chain of the codeine molecule. DHC exerts its analgesic action through affinity to mu, kappa and delta opioid receptors. After oral administration, 60 mg DHC analgesic activity is similar to 10 mg of morphine [4]. DHC and its metabolites: dihydromorphine, nordihydrocodeine and dihydrocodeine-6-glucuronide display analgesic activity mostly through mu opioid receptors activation [5]. DHC is available in CR tablets for oral administration. To our knowledge up to date no clinical studies in patients with cancer pain compared these analgesics. Quality of life (QL) assessment is increasingly important issue in patients with cancer pain. The aim of the

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3 study was to explore the impact of tramadol and DHC treatment on QL of  
4 patients with nociceptive cancer pain.  
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### 7 8 **Patients and methods**

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10 A randomized, cross-over, clinical study of patients treated either with  
11 CR tramadol (15 patients) or CR DHC tablets (15 patients) for 7 days;  
12 after this period drugs switched for another 7 days of treatment. All  
13 patients were treated at one in-patient palliative medicine unit; patients  
14 were recruited within the period of January 2007 – June 2008. To enter  
15 the study patients had to fulfill all inclusion criteria: cancer diagnosis, age  
16 over 18, opioid-naive, no history of drugs abuse, oral route of drug  
17 administration, ability of normal communication and filling questionnaires,  
18 nociceptive baseline pain intensity (VAS: 0 – no pain, 100 – the worst  
19 possible pain) over 40 during non-opioids (NSAIDs, paracetamol,  
20 metamizol) therapy, no renal impairment, if woman not pregnant and no  
21 lactation. Visceral pain was diagnosed in 17 patients, somatic in 13: in 9  
22 bone, in 4 somatic from soft tissues and from the skin. Primary tumor  
23 localization was as follows: lung (4 patients), colon (4), stomach (3) and  
24 pallatinal tonsil (2); in one patient pharynx, esophagus, gall bladder,  
25 pancreas, thyroid and suprarenal glands, kidney, prostate, breast, skin,  
26 skin melanoma, myelodysplastic syndrome, Hodgkin disease, ovary,  
27 abdominal and pelvic tumors and bone metastases from unknown  
28 primary site.  
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38 Equianalgesic dose ratio of tramadol to DHC was 5:3 when drugs were  
39 switched after 7 days of the treatment (table 1) [6,7]. The starting dose of  
40 CR tramadol was 100 mg b.i.d., CR DHC 60 mg b.i.d. titrated according  
41 to the scheme (tab. 1) to satisfactory analgesia defined as pain intensity  
42 less than 40 or decrease by at least 20 (VAS). The maximal daily doses  
43 were for tramadol 600 mg and for DHC 360 mg. In case satisfactory  
44 analgesia was not achieved the treatment was stopped, patients were  
45 switched to strong opioids. Previous treatment with NSAIDs,  
46 paracetamol or metamizol was allowed. Patients did not receive  
47 prophylactic antiemetics and laxatives when starting treatment with  
48 tramadol or DHC. EORTC QLQ C 30 and performance status (PS ECOG  
49 and Karnofsky) were assessed at baseline, at the 7th day (before drug  
50 switch) and on the 14th day of therapy. At study completion patients  
51 were asked about the preferred analgesic. All patients provided written,  
52 informed consent prior to the study procedures. The trial was accepted  
53 by the Regional Bioethics Committee at the Poznan University of Medical  
54 Sciences and it was performed according to the Declaration of Helsinki.  
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3 The data were statistically analysed with a licensed statistical package  
4 (Statistica PL, version 8.0®). Pain intensity in both groups was assessed  
5 by VAS (mean and standard deviation); the t-test for paired data was  
6 used to compare analgesic effects. In descriptive statistics of functional  
7 and symptom scales of the EORTC QLQ C 30 (data not shown), ECOG  
8 and Karnofsky PS means and standard error were provided. Two-way  
9 ANOVA was used for the EORTC QLQ C 30, ECOG and Karnofsky PS  
10 results analysis. PS (ECOG and Karnofsky) results during treatment  
11 were compared to baseline by the the least significant difference (LSD)  
12 test. In all analyses p-value 0.05 was considered significant.  
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## 18 Results

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21 At the entry of the trial 40 patients were recruited; thirty completed the  
22 study. From 10 patients who dropped out (data not included into results)  
23 four (1 from tramadol and three from DHC group) deteriorated during the  
24 first 7 days and could not received drugs orally, four patients treated with  
25 tramadol (tramadol/DHC group) and 2 treated with DHC (DHC/tramadol  
26 group) did not achieve satisfactory analgesia during titration (fig. 1). The  
27 mean age of patients was  $70.47 \pm 8.97$ ; there were 19 women and 11  
28 men. Results regarding adverse effects based on the modified ESAS  
29 (Edmonton Symptom Assessment System with two additional scales for  
30 vomiting and constipation) were reported in another paper [8]. No serious  
31 adverse events were observed with tramadol and with DHC treatment.  
32 The daily tramadol doses were  $286.67 \pm 157.35$  mg and  $256.20 \pm 109.33$   
33 mg; for DHC  $138.87 \pm 40.77$  mg and  $172.53 \pm 95.19$  mg on the 7<sup>th</sup> and  
34 on the 14<sup>th</sup> day of the treatment respectively. The mean pain intensity at  
35 baseline was  $63.07 \pm 13.48$  for tramadol and  $57.73 \pm 8.40$  for DHC ( $p >$   
36  $0.2$ ). During all but two days DHC analgesic effect was superior to  
37 tramadol (tab. 2). More patients in the tramadol group (12) than in the  
38 DHC group (8 patients) used rescue analgesics. There were 19 patients  
39 who preferred DHC treatment and 4 patients in favour of tramadol  
40 therapy; 7 patients assessed both analgesics as equally effective.  
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50 ANOVA results for functional scales of EORTC QLQ C 30 are shown  
51 (tab. 3). No drug effect was observed. There was no treatment time  
52 effect in physical, role (work), cognitive, and social functioning. However  
53 treatment time effect was observed in emotional functioning ( $p < 0.002$ )  
54 and global QL ( $p < 0.001$ ). There was no drug and treatment time  
55 interaction effect in physical, role (work) and social functioning but  
56 significant effect in cognitive functioning ( $p = 0.05$ ), emotional functioning  
57 ( $p < 0.013$ ) and global QL ( $p < 0.006$ ). Higher scores of emotional  
58 functioning in tramadol group, higher global QL and better cognitive  
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3 functioning in DHC group were observed. A trend towards better physical  
4 functioning in DHC group was noted ( $p = 0.063$  for treatment time;  $p =$   
5  $0.09$  for interaction of drug and treatment time).  
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9 ANOVA results for symptom scales of EORTC QLQ C 30 are shown  
10 (tab. 4). No drug effect was found, although in case of nausea and  
11 vomiting ( $p = 0.072$ ) and sleep ( $p = 0.06$ ) p-values were near  
12 significance. Treatment time effect was significant for fatigue ( $p < 0.036$ ),  
13 pain ( $p < 0.001$ ), sleep ( $p < 0.001$ ) and finances ( $p < 0.023$ ) with no effect  
14 in nausea and vomiting, dyspnoea, appetite, constipation and diarrhea.  
15 Interaction of drug and treatment time effect was observed for fatigue ( $p$   
16  $< 0.01$ ), nausea and vomiting ( $p < 0.001$ ), pain ( $p < 0.001$ ), sleep ( $p <$   
17  $0.005$ ), appetite ( $p < 0.039$ ) and constipation ( $p < 0.001$ ) with no effect in  
18 dyspnoea, diarrhea and finances. Less intense fatigue, pain and sleep  
19 disturbances, nausea and vomiting and better appetite in DHC group  
20 were noted. In tramadol group less constipation and financial problems  
21 were observed. No differences in dyspnoea and diarrhoea were found.  
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29 ECOG PS of all patients deteriorated comparing baseline with day 7 ( $p =$   
30  $0.008$ ) and with day 14 ( $p = 0.001$ ) (tab. 5). ANOVA revealed treatment  
31 time effect ( $p < 0.001$ ) with no drug and no drug and treatment time  
32 interaction effect (tab. 6). No differences were found in ECOG PS  
33 between tramadol and DHC groups at baseline ( $p > 0.2$ ), day 7 ( $p > 0.6$ )  
34 and day 14 ( $p > 0.27$ ; LSD test). Karnofsky PS of all patients deteriorated  
35 comparing baseline with day 14 ( $p = 0.001$ ). A trend was observed  
36 between baseline and day 7 ( $p = 0.062$ ) (tab. 5). ANOVA revealed  
37 treatment time effect ( $p < 0.001$ ) and a trend ( $p = 0.087$ ) of drug and  
38 treatment time interaction with no drug influence (tab. 6). No differences  
39 were found in Karnofsky PS between tramadol and DHC groups at  
40 baseline ( $p > 0.61$ ), day 7 ( $p > 0.92$ ) and day 14 ( $p > 0.61$ ; LSD test).  
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## 46 Discussion

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49 To our knowledge no studies were performed to date comparing  
50 tramadol with DHC in patients with cancer pain. We observed better  
51 analgesic effect of DHC. A superior DHC analgesia was demonstrated in  
52 VAS, less consumption of rescue analgesics in DHC group and more  
53 patients who preferred DHC therapy. The study demonstrated possibility  
54 of tramadol to DHC and opposite way rotation, which in clinical practice  
55 may be indicated in case of adverse effects or insufficient analgesia  
56 during tramadol or DHC therapy using tramadol to DHC ratio for the oral  
57 route 5:3. A significant increase in daily tramadol doses (40%) and DHC  
58 doses (20%) in the first week of the treatment was observed. In the  
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3 second week daily doses were more stable taking into account the  
4 former analgesic dose at the 7<sup>th</sup> day (before switch) and the ratio used  
5 for drug rotation.  
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9 Tramadol and DHC were compared in few studies. Hummel et al. in a  
10 double-blind, cross-over, placebo-controlled experimental study  
11 demonstrated both drugs to be more effective when administered in the  
12 evening than in the morning; no equianalgesic tramadol/DHC dose was  
13 established [17]. Wilder – Smith et al. compared CR tramadol with CR  
14 DHC in osteoarthritis pain not responding to NSAIDs. Dose calculation  
15 was the same as in our study (CR tramadol 100 mg b.i.d. corresponded  
16 to CR DHC 60 mg b.i.d.). Analgesia was similar but tramadol caused  
17 more adverse effects and less constipation. This trial did not comprised  
18 QL evaluation and had a parallel design. Mean daily doses of analgesics  
19 were stable over the study period (209 mg and 203 mg for CR tramadol;  
20 129 mg and 130 mg for CR DHC at the 1<sup>st</sup> and at the 28<sup>th</sup> day  
21 respectively) in contrast to the dose increments observed in our trial [6].  
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28 QL was evaluated by EORTC QLQ C 30 an instrument with sound  
29 psychometric values [18] adapted in Poland [19]. In functional scales  
30 better global QL was associated with DHC and better emotional  
31 functioning with tramadol (treatment time effect and interaction of drug  
32 and treatment time). Better cognitive functioning was connected with  
33 DHC (interaction of drug and treatment time). Better global QL observed  
34 in patients treated with DHC might be a consequence of better  
35 analgesia, less fatigue, nausea and vomiting, and sleep disturbance in  
36 this group. Better emotional functioning in patients treated with tramadol  
37 might be connected with a possible antidepressant tramadol effect  
38 observed in some experimental studies [20] and less constipation [21]. A  
39 trend of better physical functioning in DHC group was noted ( $p = 0.063$   
40 for treatment time effect;  $p = 0.09$  for interaction of drug and treatment  
41 time). There were no differences in role (work) and social functioning.  
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49 In symptom scales DHC therapy was associated with less pain, fatigue  
50 and sleep disturbance (treatment time effect and interaction of drug and  
51 treatment time), less nausea and vomiting, better appetite (interaction of  
52 drug and treatment time). Less constipation (interaction of drug and  
53 treatment time) and less financial problems (treatment time effect) were  
54 connected with tramadol therapy. No differences in dyspnoea and  
55 diarrhea were observed. Results of EORTC QLQ C 30 symptom scales  
56 are similar to those of modified ESAS, which comprised two additional  
57 scales for constipation and vomiting assessment [8]. This is the case for  
58 better analgesia and less intense nausea during DHC administration and  
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3 less constipation during tramadol treatment. The results might be  
4 associated with different mode of action of the drugs: tramadol displays  
5 significant non-opioid component [21] while DHC comparing to tramadol  
6 has significantly stronger affinity to mu opioid receptors [4] and thus may  
7 cause more intense constipation [5]. Nausea which is the most common  
8 tramadol adverse effect is connected with serotonin level increase [22].  
9 All patients did not receive prophylactic antiemetic and laxative, which  
10 would influence the results. Patients treated with DHC experienced less  
11 sleep disturbance, which might be connected with better analgesia and  
12 less fatigue. Opposite to ESAS results no differences in dyspnoea  
13 measured by EORTC QLQ C 30 were observed in this study. In finances  
14 less problems in tramadol group was not connected with the analgesic  
15 type (both drugs were provided free of charge to all patients) but rather  
16 with patients' social situation.  
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24 Differences observed in QL may suggest prescription practice.  
25 Prophylactic antiemetic administration in patients starting tramadol and  
26 laxative therapy in patients commencing DHC should be considered.  
27 Laxatives administration in patients treated with tramadol may rely on the  
28 individual assessment of constipation risk as tramadol role is negligible  
29 with this regard [23]. Similar individual approach may concern antiemetic  
30 use when starting DHC. ECOG [24] and Karnofsky [25] PS was low and  
31 decreased due to general deterioration during the study period. A  
32 significant decrease of activity was the treatment time but not drug effect  
33 or drug and treatment time interaction. No differences in PS between  
34 patients treated with tramadol and DHC were found.  
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41 The results of the study should be interpreted with significant caution as  
42 we were not able to demonstrate drug effect in any of the EORTC QLQ  
43 C 30 functional or symptom scales, ECOG and Karnofsky PS. The  
44 treatment period with each analgesic was 7 days only. Another limitation  
45 of the study was non-blinded design and lack of wash-out period, which  
46 might have influenced the results after drug switch; however the latter  
47 approach might be justified by ethical reasons in cancer pain  
48 management. Patients with neuropathic pain component were excluded  
49 as they usually need strong opioids and adjuvant analgesics  
50 administration. The number of patients recruited was small; thus the  
51 results should be replicated in a controlled study with longer follow up.  
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57 In spite of these limitations to our knowledge this is the first clinical study  
58 evaluating the influence of CR tramadol and CR DHC treatment on QL of  
59 patients with cancer pain. To conclude in functional scales DHC  
60 treatment was associated with better global QL and cognitive functioning

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3 and a trend of better physical functioning; tramadol therapy was  
4 connected with better emotional functioning; no differences in role and  
5 social functioning were found. In symptom scales DHC therapy was  
6 associated with better analgesia, less fatigue, sleep disturbances,  
7 nausea and vomiting, better appetite while tramadol treatment was  
8 connected with less constipation and financial problems; no differences  
9 in dyspnoea and diarrhea were found. All these differences were due to  
10 treatment time effect or drug and treatment time interaction with no drug  
11 influence. No differences in PS between tramadol and DHC treatment  
12 were found; in both groups ECOG and Karnofsky PS deteriorated as a  
13 result of the treatment time effect with no drug influence observed.  
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21 interest connected with the article.  
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Tab. 1. Equianalgesic doses of CR tramadol and CR DHC when drugs switched after 7 days of the treatment

Tramadol CR	DHC CR
2 x 100 mg	2 x 60 mg
2 x 150 mg	2 x 90 mg
2 x 200 mg	2 x 120 mg
2 x 300 mg	2 x 180 mg

CR – controlled release tablets

Tab. 2. Pain intensity (VAS) at baseline (before analgesics administration, day 0), during tramadol and DHC treatment (days 1 – 14; mean and standard deviation). Higher scores mean more intense pain

Day of the treatment	Tramadol	DHC	p-value*
0	63.07 ± 13.48	57.73 ± 8.40	P > 0.2
1	38.33 ± 19.27	10.20 ± 7.73	<b>0.001</b>
2	33.40 ± 23.86	11.47 ± 11.61	<b>0.003</b>
3	38.53 ± 20.93	8.13 ± 9.96	<b>0.001</b>
4	35.40 ± 19.83	7.80 ± 10.12	<b>0.001</b>
5	35.87 ± 18.86	7.80 ± 9.64	<b>0.001</b>
6	31.20 ± 22.10	8.07 ± 8.92	<b>0.001</b>
7	38.20 ± 16.27	8.80 ± 9.41	<b>0.001</b>
Analgesic switch			
8	30.93 ± 11.83	16.67 ± 13.72	<b>0.005</b>
9	30.93 ± 10.16	15.20 ± 15.24	<b>0.002</b>
10	27,60 ± 8,81	18,73 ± 16,95	0.087
11	28.67 ± 10.93	18.80 ± 16.23	0.062
12	35.47 ± 16.18	12.87 ± 12.46	<b>0.001</b>
13	32.33 ± 20.45	11.33 ± 12.30	<b>0.002</b>
14	37.93 ± 22.63	11.93 ± 13.70	<b>0.001</b>

\* t-test for paired data

Tab. 3. Results of two-way ANOVA. Dependent variables: functional scales of EORTC QLQ C 30, independent variables: drug influence, time of QL measurement and interaction of drug and treatment time. Degree of freedom: for a drug 1, for the treatment time and interaction 2.

Functional scales of EORTC QLQ C 30	Drug influence	Treatment time effect	Drug and treatment time interaction
Physical functioning	$P > 0.240$	$P = 0.063$	$P = 0.09$
Role functioning (work)	$P > 0.2$	$P > 0.1$	$P > 0.1$
Cognitive functioning	$P > 0.783$	$P > 0.1$	<b><math>p = 0.05</math></b>
Emotional functioning	$P > 0.508$	<b><math>p &lt; 0.002</math></b>	<b><math>p &lt; 0.013</math></b>
Social functioning	$P > 0.571$	$P > 0.260$	$P > 0.260$
Global quality of life	$P > 0.827$	<b><math>p &lt; 0.001</math></b>	<b><math>p &lt; 0.006</math></b>

Tab. 4. Results of two-way ANOVA. Dependent variables: symptom scales of EORTC QLQ C 30, independent variables: drug influence, time of QL measurement and interaction of drug and treatment time. Degree of freedom: for a drug 1, for the treatment time and interaction 2.

Symptom scales of EORTC QLQ C 30	Drug influence	Treatment time effect	Drug and treatment time interaction
Fatigue	$P > 0.6$	<b><math>p &lt; 0.036</math></b>	<b><math>p &lt; 0.01</math></b>
Nausea and vomiting	$p = 0.072$	$P > 0.486$	<b><math>p &lt; 0.001</math></b>
Pain	$P > 0.558$	<b><math>p &lt; 0.001</math></b>	<b><math>p &lt; 0.001</math></b>
Dyspnoea	$P > 0.353$	$P > 0.222$	$P > 0.156$
Sleep	$p = 0.06$	<b><math>p &lt; 0.001</math></b>	<b><math>p &lt; 0.005</math></b>
Appetite	$P > 0.174$	$P > 0.26$	<b><math>p &lt; 0.039</math></b>
Constipation	$P > 0.636$	$P > 0.222$	<b><math>p &lt; 0.001</math></b>
Diarrhea	$P > 0.118$	$P > 0.437$	$P = 0.09$
Finances	$P > 0.796$	<b><math>p &lt; 0.023</math></b>	$P = 0.092$

Tab. 5. Performance status (ECOG and Karnofsky) statistical characteristics (mean, standard error) and the comparison of performance status at baseline with the treatment period

Performance status scale	Performance status assessment	Mean, standard error	p*
ECOG	0	2.90 ± 0.18	-
	1	3.10 ± 0.18	<b>0.008</b>
	2	3.20 ± 0.18	<b>0.001</b>
Karnofsky	0	5.03 ± 0.18	-
	1	4.90 ± 0.19	0.062
	2	4.77 ± 0.20	<b>0.001</b>

ECOG: Higher scores mean worse PS

Karnofsky: Higher scores mean better PS

Performance status assessment:

0 – at baseline

1 – at the 7<sup>th</sup> day of the treatment

2 – at the 14<sup>th</sup> day of the treatment

\* The least significant difference test; p-values comparing performance status during the treatment period with the baseline assessment

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Tab. 6. Results of two-way ANOVA. Dependent variables: ECOG and Karnofsky performance status, independent variables: drug influence, treatment time effect and interaction of drug and treatment time. Degree of freedom for a drug 1, for the treatment time and interaction 2

Performance status scale	Drug influence	Treatment time effect	Interaction of drug and treatment time
ECOG	$P > 0.316$	$P < 0.001$	$P > 0.162$
Karnofsky	$P > 0.516$	$P < 0.001$	$P = 0.087$

Fig. 1. CONSORT diagram of the study

