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ORIGINAL ARTICLE

Multimodal approach to therapy-related neuropathic pain in breast cancer

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Summary

Purpose: *This study evaluated the effects of the multimodal therapy (gabapentin-non steroidal anti inflammatory drug [NSAID]-morphine) on intensity and relief of treatment-related neuropathic pain in patients with breast cancer.*

Methods: *This study involved 75 breast cancer outpatients who had previously undergone anti-neoplastic therapy (surgery, chemotherapy, radiotherapy). The patients were randomly divided into 3 groups, which were formed depending on the planned analgesic therapy (gabapentin, gabapentin-NSAID, gabapentin-NSAID-morphine). Each group was a control group to itself. The pain intensity difference and scores of daily activities were collated and assessed by the modified Brief Pain Inventory (BPI) questionnaire (VAS/Likert Scale). Monitoring the additional medication and side effects optimized the therapy efficiency evaluation.*

Results: *During this 6-week study, the decrease of pain intensity was significant in all 3 groups ($p < 0.0001$). Although there was intergroup difference, it was statistically not significant ($p > 0.05$). The variant analysis of pain relief showed differences both among and within the groups in the first 3 weeks of the study ($F_1 = 7.79$, $p = 0.000$; $F_2 = 7.01$, $p = 0.001$; $F_3 = 5.49$, $p = 0.001$). The multimodal group needed the least of additional medication and the variant analysis showed a statistically significant difference ($p = 0.001$) from the 4th week of the trial period. The correlation between the increase trend of side effects and the frequency of additional medication was significant ($p < 0.05$).*

Conclusion: *The multimodal therapy ensures adequate cancer-related neuropathic pain control with minimal side effects.*

Key words: anticonvulsants, breast cancer, gabapentin, multimodal therapy, neuropathic pain

Introduction

Cancer-related neuropathic pain syndromes are common and serious complications of a patient's primary malignancy or its treatment, whether by surgery, radiation or chemotherapy [1].

In 77-80% of the cases the invasive tumor itself causes pain, but despite their successful influence on the course of the malignant disease, contemporary antineoplastic therapies cause early or delayed pain in 15-25% of the cases. The pain may compromise the patients' quality of life as well as their ability to receive effective treatment because it may result in treatment delays, dose reductions and discontinuations. In many patients there may be more than one coexisting neuropathic pain syndrome [2].

Currently, there are no agents approved for the treatment of neuropathic pain specifically associated with cancer or its treatment, and most agents that have been developed for neuropathic pain have been studied in patients with post-herpetic neuralgia or peripheral diabetic neuropathy [3,4].

Existing treatments are symptomatic rather than disease-modifying or curative. A range of therapeutic modalities is emerging, targeting a variety of mechanisms, but choosing the best target and evaluating the resulting therapies against the many types of neuropathic pain disorders is not an easy task [5].

The appearance of a pain syndrome after breast cancer therapy is much more common than it used to be thought. Besides the common conventional analgesics, the new generation of anticonvulsants are in-

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creasingly being used as drugs of choice in the control of neuropathic pain. Multimodal therapy is recommended, which implies a combination of more analgesics in smaller but adequate doses in order to achieve the desired analgesic effect and maintaining minimal side effects.

Methods

The study involved 75 outpatients who had previously gone through different therapies for breast cancer and had experienced pain of neuropathic character several months after their therapies.

Inclusion/exclusion criteria

The inclusion criteria into the study were as follows: pain intensity ≥ 5 on a VAS scale, pain duration ≥ 3 months, patients older than 18 years of age, with preserved cognitive capabilities, capable for therapy by mouth, normal renal function and no gastrointestinal complaints. The exclusion criteria were the following: previous anticonvulsant and opioid therapies, proved oversensitivity to the drugs used in the study (NSAID, morphine [M-Eslon], gabapentin), potential neuropathic states due to diabetes, herpes, alcoholism, or HIV infection.

Group randomization and drugs administered

The patients included into the study were randomly divided into groups (table of random numbers). Three groups were formed on the basis of the planned neuropathic pain therapy. Each group was a control group to itself. The registered values of the designed parameters for this study were marked at the first visit, prior to therapy (V0) and were used as starting values, and the other parameters obtained during the 6 consecutive weekly visits (V1-V6) were compared to the V0 values.

Group 1 (n=25) patients received monotherapy with gabapentin (Neurontin®, Pfizer, caps 300 mg). The initial dose of 300 mg was titrated to 900 mg, divided into 3 individual daily doses until the end of week 1 (V1) and then, in 6 consecutive weeks the dose was gradually increased to the maximum 3,600 mg/day, until reaching a satisfactory analgesic response.

Group 2 (n=25) patients received a constant daily dose of the combination of gabapentin 1200 mg and diclofen (Galenika AD, tabl 50 mg) 100 mg, which was not changed during the study. Drugs were also gradually administered in this group, from the usual initial dose of gabapentin 300 mg and diclofen 50 mg, to the planned constant dose reached until the end of week 1, i.e. before the first control visit (V1).

Group 3 (n=25) patients received a combination of 3 drugs in a constant dose throughout the study: gabapentin 900 mg, diclofen 100 mg and M-Eslon (Grunenthal GmbH, caps 30 mg) 60 mg divided into 2 or 3 individual daily doses, by gradually reaching these doses until the first control visit (V1).

Additional medication was allowed PRN: immediate release opioid medication (20 mg of morphine sulphate in 100 ml), administered by tablespoon (Tbsp); 1Tbsp=15 ml=3 mg morphine. The indication for additional medication was strictly defined and could only be administered if breakthrough pain was frequent in 2 consecutive days, and/or, only in case of group 1, when the therapy side effects occurred in such intensity that increasing the dose of the basic therapy in order to achieve satisfactory analgesic response would have led to further inconveniences.

Assessment of response

A modified questionnaire based on BPI was used in this study, which, besides pain intensity assessment, takes into consideration the influence of pain on daily activities through the following categories: general activity, mood, mobility, normal work, interpersonal relationship, sleep and enjoying life. The patients assessed their own pain intensity at V0 and at each visit (V1-V6) in a period of 6 consecutive weeks. They also assessed their own minimal, maximal and average pain intensity during the previous week (starting from V0). Pain intensity was assessed by VAS and/or the 11-point Likert scale, where 0 means "no pain", and 10 means "worst possible pain". Similarly, the VAS scale was used to assess the influence of pain on daily activities in all 7 categories respectively (0=no influence, 10=strongest possible influence). The mean value of the stated categories represents the score of the influence of pain on daily activities, which is also taken into account in the BPI questionnaire. At visits (V1-V6) the patients estimated the pain relief they had felt when compared to V0. The Pain Intensity Difference (PID) was assessed by values of 0-100%, where 0=no pain relief and 100=completely relieved pain.

In all groups, the side effects of the used medication were assessed by a Linkert-type scale, where 0=no side effects, 1=mild side effects, 2=moderate side effects and 3=severe side effects, and the consistency of side effects was expressed in percents. The protocol also included the category of "additional medication", which was numerically expressed in terms of a dose unit (Tbsp).

Statistical methods

The results were presented in Tables and Figures. Mean values and SD were calculated. ANOVA-variance analysis was done for independent samples and repetitive assessments in order to check whether there was a significant difference in inter- and intra-group variability. Mann-Whitney test was used to check the significance of the obtained differences between measurements within a group as well as between groups. Wilcoxon Signed Rank test for dependent samples was used in order to rank patients according to their subjective estimates of pain intensity. Pearson test of linear correlation was used in order to check the connection between side effects and the rescue medication for their treatment. For data processing the STATISTICA for Windows 5.0, Start soft Inc. was used. Figures and Tables were done in Microsoft Excel.

Results

The patient age ranged from 23 to 74 years (median 44). Most of the patients were in the 41-50 years age group. Each patient had undergone different therapies for breast cancer prior to study entry (surgical 11, surgical and irradiation 21, surgical and chemotherapy 12, surgical, irradiation and chemotherapy 31).

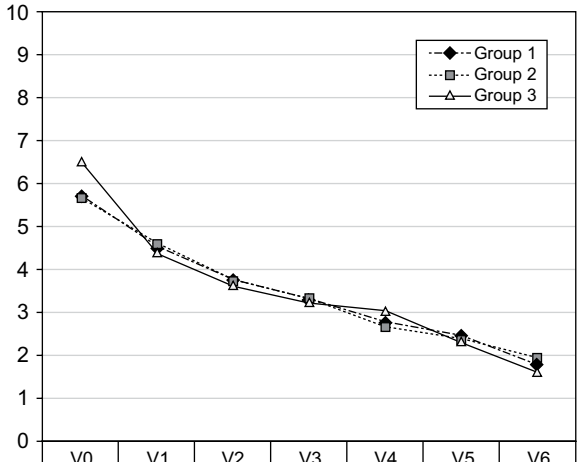
Figure 1 shows the mean values of pain assessment for each group at each visit (from V0 to V6). Having tested pain intensity by the Wilcoxon Signed Rank test for dependent samples, the following results were obtained: from V0 to V6, according to patients' subjective assessment, there was a decrease of pain intensity in all 3 groups. The difference in mean values of pain intensity from V0 to V6 for each group was statistically significant (p=0.0001). There was a difference among the groups regarding pain intensity, but this difference, tested by the Mann-Whitney test, was not statistically significant (p >0.05).

The final score of influence of pain on daily activities was obtained by averaging the measured values presented in Figure 2.

Through variance analysis, the difference in the level of influence of pain on daily activities among the groups was examined. The F test was low and ranged from 0.035 to 1.98 and was not statistically significant (p >0.05).

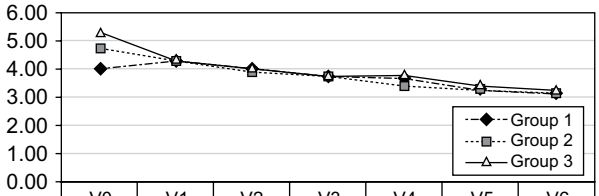
A trend for decreasing influence of pain on daily activities was observed in all 3 groups, especially in the period from V0-V1, but, generally, the decreasing trend of the scores was evenly distributed.

The variance analysis showed a significant difference both between and within groups regarding this variable during the first 3 measurements, i.e. V1, V2 and V3. The F value for the first measurement was 7.79 and was highly significant (p=0.000). As for V2, the F value was 7.01, and the difference was statistically significant (p=0.001). For the V3 measurement, the F value was 5.49 and was statistically significant (p=0.001). Other measurements also showed differences in terms of pain relief, but their statistical significance was either not high enough or there was no significance at all. Having done a *post hoc* analysis in order to establish whether the first 2 groups were also different from each other, it could be concluded that these 2 groups represented a relatively homogeneous population when compared to group 3, which had been expected to be so. Bearing in mind that all 3 groups were administered different medicament therapies, it was interesting to see how each of these 2 groups compared to the 3rd one (Figure 3). The F value for the first 3 measurements, when group 1 and group 3 were compared, ranged from 10.17 for V3 to no less than 16.97 for V1, and these differences were highly significant (p=0.000). However, the difference



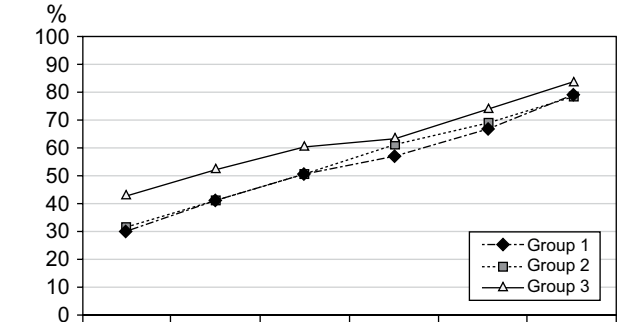
	V0	V1	V2	V3	V4	V5	V6
Group 1	5.76	4.48	3.8	3.28	2.8	2.48	1.8
Group 2	5.68	4.6	3.76	3.36	2.68	2.36	1.96
Group 3	6.52	4.4	3.64	3.24	3.04	2.32	1.64

Figure 1. Pain intensity. V: visit number.



	V0	V1	V2	V3	V4	V5	V6
Group 1	4.00	4.30	3.99	3.79	3.67	3.38	3.09
Group 2	4.73	4.25	3.93	3.76	3.41	3.26	3.14
Group 3	5.34	4.35	4.01	3.83	3.80	3.45	3.20

Figure 2. Score of influence of pain on daily activities. V: visit number.



	V1	V2	V3	V4	V5	V6
Group 1	29.2	40.8	50.2	56.8	66.4	79.0
Group 2	31.2	40.6	50.4	60.8	68.8	77.8
Group 3	42.8	52.4	60.2	63.2	73.0	83.0

Figure 3. Level of pain relief (%) per visit, per group. V: visit number.

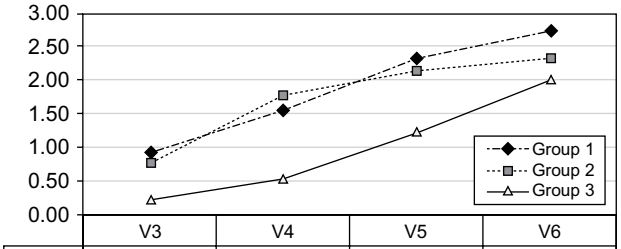
between group 2 and group 3 was somewhat smaller, yet significant (p=0.002).

The variance analysis showed that all 3 groups differed significantly, which had been expected during the study, because additional medication was administered in a strictly controlled manner, only when it was really indicated. The F test for V4 was 8.74 and was statistically significant (p=0.01) and all the time to V6, where it was 3.32 and again significant (p=0.04).

Further statistical analysis of groups 1 and 3 showed that, for V3 to V6, F values ranged from 11.79 to 6.61. The difference for all 4 values was also statistically significant (p=0.001).

Groups 3 and 2 also differed. The F value ranged from 22.61 to 7.08, and the statistical significance was p=0.000. Group 1 and group 2 were, as expected, relatively homogeneous. Group 3 needed the smallest quantity of additional medication, which only supports the fact that the variations of pain intensity were least present in this group (Figure 4).

Statistical analysis of side effects did not show any significant differences regarding the intensity of side effects between the groups (the intensity of side effects was measured by the Likert type scale, where



	V3	V4	V5	V6
Group 1	0.92	1.52	2.32	2.72
Group 2	0.76	1.76	2.12	2.32
Group 3	0.20	0.52	1.32	2.00

Figure 4. Additional medication (unit=Tbsp). V: visit number.

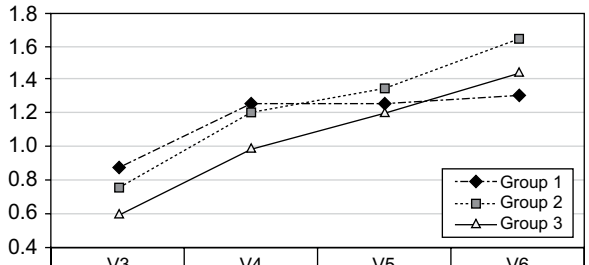
0=no side effects, 1=mild, 2=moderate and 3=severe). This result is the measure that follows the variable of additional medication (Figure 5).

It is interesting to note that the side effects "grew" in intensity as a follow-up effect with time (Figure 6).

In order to show the correlation between additional medication and side effects, the Pearson's quotient of linear correlation, which illustrates the increase of the intensity, i.e. the frequency of side effect occurrences in correlation with the frequency of additional medication administration, was used. In Table 1, the marked correlations were statistically significant according to Pearson's quotient of linear correlation ($p < 0.05$).

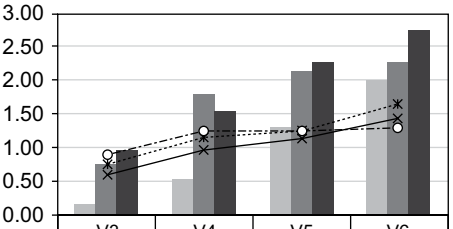
Discussion

Opioid analgesics used to be considered the only first line medication in the treatment of moderate and



	V3	V4	V5	V6
Group 1	0.84	1.24	1.24	1.32
Group 2	0.76	1.2	1.36	1.64
Group 3	0.6	0.96	1.20	1.44

Figure 5. Intensity of side effects. V: visit number.



	V3	V4	V5	V6
Group 3 Additional Medication	0.20	0.52	1.32	2.00
Group 2 Additional Medication	0.76	1.76	2.12	2.32
Group 1 Additional Medication	0.92	1.52	2.32	2.72
Group 3 Side Effects	0.6	0.96	1.20	1.44
Group 2 Side Effects	0.76	1.2	1.36	1.64
Group 1 Side Effects	0.84	1.24	1.24	1.32

Figure 6. Relation between additional medication and side effects. V: visit number.

Table 1. Correlation between additional medication and side effects (whole sample observed)

Additional medication	*Side effects* V3	V4	V5	V6
V3	0.28*	0.36*	0.34*	0.33*
V4	0.15	0.27*	0.30*	0.35*
V5	0.18	0.20	0.44*	0.47*
V6	0.15	0.11	0.33*	0.43*

*values that are statistically significant (Pearson's test). V: visit number

severe neuropathic pain of malignant aetiology. However, their role in treating neuropathic pain appearing after an antineoplastic therapy is controversial.

The efficacy of gabapentin, a new generation anticonvulsant, was established in diabetic neuropathy [6] and post-herpetic neuralgia [7]. A research by Caraceni et al.[8] and Lossignol et al. [9] points out the favorable activity, a good, safe profile and a fast onset of analgesic effect of gabapentin on neuropathic pain of direct malignant origin. Today, opioids and gabapentin are prescribed as first line treatment of neuropathic pain. The maximum tolerable dose of these drugs, given as monotherapy, reduces pain intensity by only 26-38% because of their incomplete efficacy and/or because of their dose-dependent side effects. The combination of gabapentin and morphine, in terms of their mechanism of action, may have an additive or synergistic effect, i.e. it improves the efficacy of smaller doses of these two drugs with more moderate side effects than when using each one of these drugs individually [10]. The analgesic effect of gabapentin is resistant to opioid antagonism, and its re-administration does not lead to analgesic tolerance [10,11]. Preclinical studies support this and argue that there may be an additional interaction between gabapentin and morphine, and opioid tolerance can be prevented by the usage of gabapentin [12,13]. Besides sedation effects, the recognized side effects connected to opioids are very rare in the therapy with gabapentin, which only supports the fact that most of the side effects will not appear if these two drugs are combined. Therefore, the combination of morphine and gabapentin is believed to enable a better analgesic than sedative effect [14].

The results in this study showed a statistically significant (p=0.0001) drop of the average value of pain intensity, measured by the VAS/Likert Scale until the end of the investigation period (V6) for all 3 study groups. The largest decrease of pain intensity was observed at the first control visit (V1), which, in all groups amounted to: G1=1.28, G2=1.08, G3=2.12. This was to be expected because the patients had had no previous analgesic therapy, or they had, in isolated cases, been taking NSAID. Throughout the 5 consecutive weeks (V2-V6), the median pain intensity also fell in all study groups (the average decrease per group was: G1=0.53, G2=0.52, G3=0.55). There was a difference among the groups but without statistical significance ($p > 0.05$). The largest decrease of pain intensity at the end of the study period, though, was observed in group 3, the multimodal group, where the patients were given gabapentin, morphine and NSAID. Therefore it can be concluded that the multimodal medication offers good pain control.

The BPI obtained results showed a trend of decreasing influence of pain on everyday activities in each group. Generally, the intergroup analysis showed decreasing trend scores evenly distributed in all groups. Through variance analysis, the level of influence of pain on daily activities was checked among the study groups. The F test was low (0.035 -1.98) and was not statistically significant ($p > 0.05$). These results did not correspond to the findings of Ross et al., which suggest significant decrease of influence of pain on daily activities ($p < 0.003$), neither to the results of Gilron et al., which point out the influence of pain intensity decrease on mood ($p < 0.001$) [15,16].

The results of this study have shown that there is a difference in the level of pain relief in all 3 groups, especially in the first 3 weeks (the statistical significance was p=0.000 for V1, and p=0.001 for V2 and V3). Group 3 achieved higher level of pain relief (42.8%) already during the first week, and after the second week all 3 groups marked more than 50% of pain relief, only to reach significant analgesia in all 3 groups at the end of the study, namely, pain relief resulted in: group 1=79%, group 2=77.8%, and group 3=83%. The variance analysis showed high F values (F=10.17 for V3 and F=16.97 for V1) for the first 3 measurements when our attention was focused on group 1 and group 3 patients; these differences were statistically significant (p=0.000). The difference between the group 2 and group 3 was somewhat smaller, yet still statistically significant (p=0.002).

In this study, the differences in the subjective assessment of pain intensity were not as large as it was the case with the subjective assessment of pain relief. These significant discrepancies among the patients point to the fact that the decrease of pain intensity and the impression of absence of pain in group 3 led them to this subjective assessment of great relief. This fact is sufficient enough for us to decide about the type of therapy: the combination of the anticonvulsant (gabapentin), sustained release morphine (M-Eslon) and NSAID (diclofen), which so far proved to be the best choice of medication.

The efficiency of therapy unavoidably also depends on the constant monitoring of toxicity of the administered drugs as well as the side effects they may cause. The obtained results indicate that in group 1 the dose of gabapentin was being successively increased until the maximum dose was reached (2400 mg/day, 1608 mg/day on average) depending on the side effects, along with the maximum dose of additional medication, of morphine syrup, 8.16 mg (5.16 mg on average). The side effects most often reported were sleepiness (24%), dizziness (20%), dry mouth (12%), headache (8%) and nausea (8%) of mild or moderate intensity. These side effects did not require any dose reductions or therapy discontinuation.

Groups 2 and 3 received a combined therapy with a determined constant dose of drugs (group 2=gabapentin 1200 mg, NSAID 100 mg; group 3= gabapentin 900 mg, morphine 60 mg and NSAID 100 mg). Because of the above mentioned synergistic effect of gabapentin and morphine, it is interesting to note that in group 3 the maximum dose of additional medication was 6 mg/day (4.53 mg on average). The side effects most often reported in this group were constipation (16%), nausea (12%), sleepiness (12%) and dizziness (8%). These side effects were also mild and moderate. The usual doses of antiemetic drugs and laxatives solved these problems and there was no need for therapy discontinuation or dose reductions.

The correlation between additional medication and side effects is also worth mentioning. It was statistically significant ($p < 0.05$) in all 3 groups. It is true that side effects occurred in different time intervals in different groups. However, it is no coincidence that group 3 experienced them the latest, during week 5. This also confirmed the hypothesis of this study that the multimodal therapy with small doses of medication provides good analgesia with the least side effects.

The obtained results are impressive enough, and they unambiguously lead to the conclusion that the multimodal therapy is the best choice. Further investigation on a larger sample and follow-up visits would be most valuable because more patients would be investigated for a longer time period. In that case, it could be observed how the quality of life would probably improve through fitting the disease and/or pain into patients' daily lives and controlling pain within the reference boundaries. Only then we could be absolutely positive that by reducing the intensity of pain we simultaneously reduce its influence on everyday activities which eventually offers better quality of life.

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