

## Kanser hastalarında WHO analjezik basamak tedavisine göre ağrı tedavisi. Bir merkezin sekiz yıllık deneyimi

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### ÖZET

Bu çalışmada, anesteziyoloji ağrı bölümüne kabul edilen kanser hastalarının ağrı tedavisinde uygulanan Dünya Sağlık Örgütü'nün analjezik basamak tedavisi ve diğer tedavi yöntemlerinin sonuçlarını değerlendirdik. Hasta özellikleri, hastaların kanser patolojilerine göre dağılımı, analjezik basamak tedavisine göre ilk ve son dağılımları, diğer invaziv ve noninvaziv tedavi yöntemleri, tedaviye bağlı yan etkiler ve diğer veriler incelenmiştir. 475 hastanın 416'sı (% 87.5) WHO analjezik basamak tedavisi ile, 57 hasta ise (% 12) invaziv girişimlerle tedavi edildi. I. basamakta 49 (% 11.77), II. basamakta 307 (% 73.79), III. basamakta ise 60 (% 14.42) hasta başarı ile tedavi edilmiştir. 416 hastanın 181'i (% 43.50) antikonvülsan veya nöroleptik, 341 (%81.97) hasta ise antideprasan kullanmıştır. 31 (%7.5) hastada, analjezik basamak tedavisinin etkinliğini artırmak için non invaziv veya invaziv tedavi yöntemleri basamak tedavisine eklendi. Tüm çalışma sürecinde hastaların % 17'si yan etki bildirdi. Hastaların ortalama takip süreleri  $42 \pm 109.7$  gün, ortalama görüşme sayıları  $5.6 \pm 7.6$  kez, en uzun takip süresi 1380 gün, aynı hasta ile en çok görüşme sayısı ise 68 oldu. Sonuç olarak, Dünya sağlık örgütü analjezik basamak tedavisine sadık kalınarak, uygun hasta için uygun analjezik ve adjuvanların uygun oral dozlarının verilmesi ile hastaların büyük çoğunluğu başarı ile tedavi edilebileceği kanısındayız.

**Anahtar Kelimeler:** Kanser ağrısı, ağrı tedavisi, Dünya sağlık örgütü, Analjezik basamak tedavisi, opiyat.

### SUMMARY

**Pain treatment practice according to the WHO analgesic ladder in cancer patients: eight years experience of a single center.**

In this study we evaluated the results of pain treatment practices according to the World Health Organization analgesic ladder treatment, and other treatment modalities in cancer patients who were admitted to an anesthesiology-based pain service. Patient characteristics, distribution of the patients according to the primary pathologic sites, initial and last distribution of the patients according to analgesic ladder treatment, other invasive or non-invasive treatment modalities, side effects, and other data related with the patients were examined. 416 of 475 (87.5%) patients were treated using the WHO analgesic ladder treatment, 57 patients (12 %) were treated by invasive techniques. The number of successfully treated patients in step I, II and III were 49 (11.77%), 307 (73.79%) and 60 (14.42) respectively. 181 of 416 (43.50%) patients used anticonvulsants or neuroleptics, 341 of 416 (81.97%) patients used antidepressants. In 31 of 416 patients (7.5%), non-invasive or invasive treatment modalities had become necessary to augment the WHO analgesic ladder treatment. Over the entire treatment period, side effects were reported in 17.05% of the patients. The follow-up time for the patients was  $42 \pm 109.7$  days, the mean interview number was  $5.6 \pm 7.6$ , the longest follow-up time was 1380 days, and the maximum number of the interviews made by the same patient was 68. In conclusion, we think that, using the World Health Organization analgesic ladder treatment and administering appropriate analgesics and adjuvants in appropriate oral doses determined for appropriate subjects could successfully treat a great number of these patients.

**Key words:** Cancer pain, pain treatment, WHO, Analgesic Ladder treatment, Opioid

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## Introduction

Unrelieved cancer pain is widely recognized as an international health problem. At least one-third of newly diagnosed cancer patients and two-third of the patients with advanced disease report pain (Mercadante and Fulfaro 2005, Quigley 2005, Simmonds 1997).

Various treatment modalities and therapeutic options are available for clinicians to treat cancer pain. The most common method proposed by the World Health Organization (WHO) for cancer pain relief consist of guidelines for a three step treatment from non-opioid to weak and strong opioids according to need (Mercadante and Fulfaro 2005, World Health Organization 1986) Opioids alone, or co-administered with non-opioid analgesic and adjuvant drugs, can relieve pain caused by cancer in a majority of patients (Marinangeli et al. 2004, Breivik 2001). However, survey results in the developed countries have shown that the management of chronic pain is far from satisfactory (Mueller 2001).

The purpose of this study was to evaluate the results of pain treatment practices according to the WHO analgesic ladder treatment and other treatment modalities in cancer patients who were admitted to our department.

## Methods

A retrospective study was carried out reviewing the records of 475 cancer patients treated for moderate or severe cancer pain during the period from October 1992 to 2001 by the Pain Therapy Service of the Department of Anesthesiology, GATA and School of Medicine in Ankara.

This study examined patient characteristics, distribution of the patients according to the primary pathologic sites, initial and last distribution of the patients according to the WHO analgesic ladder treatment, other invasive or non-invasive treatment modalities, side effects of the drugs and the treatments, and other data related to the patients. All the data about the patients and treatment modalities were recorded and evaluated, from the first examination to the end of the treatment or death of the patient.

## Patient Evaluation and Pain Management

Before beginning the treatment of a cancer patient, a comprehensive evaluation (complete

history including general medical and oncologic history, psychologic and social evaluation) and pain assessment (pain history, quality, intensity, duration etc.) were performed by the staff anesthesiologist.

Once all of the information was obtained, the individualized detailed treatment plan was discussed and decided upon by the patient, his or her relatives and the senior anesthesiologist. Subsequent follow-up of the patient was performed when possible by the same anesthesiologist to provide close collaboration and convince between each other.

The mainstay of the WHO guidelines is a three step ladder of analgesic and adjuvant drug use with administration of the drug by mouth, by clock (i.e. at regular intervals), and at exact doses, which are determined individually (World Health Organization. Cancer Pain Relief 1986). Adjuvant drugs are added to the nonopioid or opioid drugs if required for specific indications.

Three step analgesia was performed according to the WHO guidelines for the pain treatment of the cancer patients who were appropriate for use of the analgesic ladder. Assessment of pain intensity and pain relief was made using standard visual analogue scales (VAS, 10 cm) and on a four-point verbal rating scale (VRS, none, mild, moderate, severe) or pain relief scale. We selected whichever one of them the patient could relate to and understand.

The common side effects of the analgesic drugs and control of these were explained to the patient and his or her relatives. Appropriate antiemetics and/or anticonstipation drugs or special diets were added to the treatment according to need.

The second examination and pain assessment of the patient was conducted on the second or third day of the treatment and the treatment plan of the patient was changed, if required. Pain control was achieved within a short period of time with maintenance of relief as the goal. The subsequent interviews and assessments were done face to face if possible; if not, the patient or his or her relatives communicated with us by telephone when necessary. Afterwards, all the results and data about the patient and the treatment were recorded to the patient's medical record from the

first examination to the end of the treatment or death of the patient.

### Results

The demographic data and treatment modalities of the cancer patients are presented in Table 1. 416 of 475 (87.5%) patients were treated using the WHO analgesic ladder, and 57 patients (12%) were treated by invasive treatment modalities (epidural, spinal catheterization) because of undergoing oncology surgery for palliative treatment. Their pain treatment also scheduled for postoperative analgesia. Two patients were sent to other algology centers for failure of pain relief (VAS > 5, 7 cm). From the distribution of primary pathologic sites (Table 2), it appears that pain caused by lung cancer, the most common group of malignancy, is predominant.

**Table 1.** Patient demographics and initial treatment modalities

Patient number	475
Female	178 (37.40%)
Male	297 (62.50%)
Mean Age ( $\pm$ SD)	55.9 $\pm$ 15.4
WHO sequential ladder	416 (87.50%)
Invasive technique	57 (12%)
None	2 (0.42)

The distribution of the patients at the beginning and the last distribution at the end of the treatment or end of survival of 416 patients according to the steps of the analgesic ladder are presented in Table 3. During the treatment period, the number of patients treated in step I decreased, whereas those in step III increased progressively. 28 of 77 patients in the first step were advanced to the second step and 40 of 347 (319+28 from first step) patients in the second step were advanced to the third step due to insufficient analgesia (VAS>3 cm). Pain intensity decreased significantly within one week from the time of admission, and this decrease was maintained during the treatment period or to the end of life. Dosages were kept as low as possible initially but were increased when patients reported that the intensity of pain was unacceptable (VAS>3 cm). Adjuvant drugs were added to the treatment protocol for specific indications in 82% of the patients. 181 of 416 (43.5%) patients used anticonvulsants and 341 of 416 (81.97%) patients

**Table 2:** Distribution of the primary pathologic sites of the patients

Primary malignancy	Number	Percentage
Esophagus	9	1.89
Stomach	42	8.84
Pancreas	39	8.21
Liver- gallbladder	16	3.36
Colon	43	9.05
Rectum	33	6.94
Prostate	26	5.47
Bladder	5	1.05
Uterine cervix over	48	10.10
Renal	17	3.57
Bone	20	4.21
Breast	27	5.68
Skin	3	0.63
Lung	92	19.36
Lymphoma	6	1.26
Head	3	0.63
Neck	21	4.42
Others	25	5.26
Total	475	100

used antidepressants. 301 of 416 (72.35%) patients used antidepressant and anticonvulsants together.

In 31 of 416 patients, non-invasive or invasive treatment modalities had become necessary to augment the WHO analgesic ladder treatment (Table 4). 2 patients were sent to other algology centers due to hypersensitivity to all analgesic drugs. Pain treatment of five patients was ended because of cure of their primary oncologic disease and pain. Side effects reported during all the pain therapy are presented in Table 5.

The follow-up time of the patients was  $42 \pm 109.7$  (Mean  $\pm$  SD) days, the mean interview number was  $5.6 \pm 7.6$ , the longest follow-up time was 1380 days, and the number of the interviews made by the same patient was at most 68.

**Table 3:** The initial and last distribution of the patients according to WHO analgesic ladder

Analgesic Ladder	Initial Distribution		Last Distribution	
	Number	Percentage	Number	Percentage
Step I	77	18.50	49	11.77
Step II	319	76.68	307	73.79
Step III	20	4.80	60	14.42
Total	416	100	416	100

**Table 4.** Number and percent of 416 patients taking different non-invasive or invasive treatment modalities

Type of treatment	Number	Percentage
TENS	8	1.92
Epidural	16	3.86
Peripheral nerve block	4	0.96
Trigger point	3	0.72
Total	31	7.45

## Discussion

In our study, the demographic findings of the patients have showed accordance with the similar study of Ventafridda and et al. (1987). The male/female ratio was 62.5/37.4% and mean of the ages of the patients was  $55.9 \pm 15.4$ ; as for the mentioned study, the values were 62/38% and  $57.5 \pm 8.4$  respectively.

The success rate of our treatment based on the WHO analgesic ladder was 87.5%. Ventafridda et al. (1987) and Zech et al. (1995) reported the rates as 71% and 88 % respectively.

The percentage of the patients who started the therapy from the first step of the WHO analgesic ladder was 18.5%, but the ratio of the patients who were treated only in this step was 11.87 %, whereas Ventafridda et al. (1987), Zech et al. (1995) and Zimmermann (1991) reported the ratio of the patients who were treated only in first step as 11.1 %, 11 % and 15 % respectively.

Non-opioid analgesics, including acetaminophen, aspirin, and nonsteroid anti-inflammatory drugs

(NSAIDs) can be useful analgesics at all stages of cancer pain (Oxberry and Simpson 2005, Lucas and Lipman 2002). It was reported that naproxen, diclofenac and indomethacin were highly effective (70.9%, 67.3% and 63.6% respectively) in pain relief and were relatively well tolerated (Ventafridda et al.1990). It was also reported that NSAIDs should be considered as the first-choice drugs in the initial treatment of cancer pain. In another study it was found that the analgesic efficacy of 2 grams of dipyron every 8 hours was similar to that of 10 mg of morphine every 4 hours for the treatment of cancer pain (Rodriguez et al.1994). Furthermore, it was reported that cancer pain, especially due to stimulation of tissues having free nerve ends like serous membranes, periosteum, joint, muscle fascia, could be completely controlled easily by non-opiates (Droure et al. 1997, Ventafridda et al. 1990). However, it is well-known that nonopioids can be administered only for a limited period of time because of a ceiling effect on their analgesic efficacy and an increasing incidence of side effects (Rodriguez et al.1994, Ventafridda et al.1990).

If a non-narcotic is not effective or poorly tolerated, a narcotic analgesic is considered as an alternative drug to manage pain (Foley and Inturrisi 1987). In this study, weak opiates were added to the treatment regimen due to insufficient analgesia in 28 of a total of 77 (36.3%) patients who started from the first step of the therapy. This ratio was reported as 52% in another study (Ventafridda et al. 1987). Although the number of patients for whom initial treatments started from the first step was expected to be higher, the ratio (18%) was lower than the ratio of the patients in the second step (76.6%). The reasons for this finding were that 1) previously the existing treatments were not given according to the WHO



method and/or 2) the inappropriate use of medicines (a spectrum range from nonopioids to strong opioids) by the patients referred to our observation.

The number of successfully treated patients in the second step was 307 (73.79%) during the therapy period. Our patient success rate was higher than Zech's (1995) (31%) and Zimmerman's (1991) (15%) rates in this step. Ventafridda et al. (1987) and Zech et al. (1995) reported the ratio of the patients treated in the third step as 68% and 49% respectively. The ratio of the patients treated in this step was lower in our study (14.42 %) than the above-mentioned studies. The possible reason of these different rates in second and third steps compared to other studies could be the use of maximum possible dosage of weak opiates for our patients who were in the second step. In our clinical practice, codeine was used as the weak opiate. Codeine is often used in combination with other drugs. Equal dosages of codeine and caffeine were combined and produced as 20+20, 40+40, 60+60, and 80+80 mg capsules in the Pharmacology and Pharmaceutics Department of our hospital. Caffeine is a psychostimulant and used as an adjuvant analgesic for enhancing the analgesic efficacy of codeine and also for decreasing sedation due to opioid analgesia (Practice Guidelines for Cancer Pain Management. A Report by the American Society of Anaesthesiologists Task Force on Pain Management, Cancer Pain Section 1996). The codeine-caffeine combination provided the opportunity to select dosages from 20 mg to a maximum dosage according to individual need. Furthermore weak opioids are more freely available and are expected to have a better side-effect profile. We consider that it is possible to prepare codeine-caffeine combination easily all over the developed and developing countries according to required dosage for the patient that physicians ordered. Grond and Meuser (1998) also underlined that the use of weak opioids has great educational impact and has helped spread the use of the WHO guidelines.

Strong opiates are effective in treatment of cancer pain (Marinangeli et al. 2004, Brooks et al. 1989). Morphine by mouth is still recommended as the standard "step III" opioid (Quigley 2005, Breivik 2001). Cancer pain especially can be treated by slow-released morphine tablets used

orally at intervals of 8 to 12 hours with a success rate of 90% (Zylicz and Twycross 1991). Other routes may be useful, however, in selected patients (Quigley 2005). Most clinical experience with the highly lipophilic opioid fentanyl citrate for cancer pain has been with the transdermal patch (Portenoy and Lesage 1999). In 1998, the FDA approved a new formulation, oral transmucosal fentanyl citrate. It is indicated for the treatment of breakthrough pain in patients who are already receiving and are tolerant of opioid therapy (Lucas and Lipman 2002). Even today, in most countries including developed countries, strong opiates are not used appropriately for many reasons such as insufficient knowledge about clinical usage, inadequate communication between doctors and patients, fear of morphine addiction, procurement problems, and side effects etc. (Foley and Inturrisi 1995). These problems are surely among the reasons for ineffective management of cancer pain. The failure rate of cancer pain therapy due to these situations was reported as 30-80% (Ventafridda et al.1987). The failure due to insufficient opiate dosage was reported as 42%, and over-extension of intervals between dosages as 66% (Zimmermann 1991).

**Table 5.** Side effect profile of 475 patients

Side-effects	Number	Percentage
Constipation	23	4.8
Nausea and vomiting	25	5.26
Drowsiness	28	5.89
Urinary retention	4	0.82
Tolerance	1	0.21
Total	81	17.05

Adjuvant drugs can be used in all three steps and this provides a great advantage in therapy (Drouin et al.1997, Ventafridda et al. 1987). Neuropathic pain develops in more than one third of patients with cancer. In a study involving 1095 patients with severe cancer pain, 40% of patients reported symptoms that were consistent with neuropathic pain in addition to their somatic and visceral pain (Lucas and Lipman 2002). Tricyclic antidepressants and anticonvulsants are first-line therapy for neuropathic pain. In this study, anticonvulsant drugs were added to the

treatment regimen in 43.5% of the patients and antidepressant drugs in 81.97% of the patients. In Ventafridda's study (1987) 79% of patients used adjuvant drugs; 66.01% narcotics and benzodiazepines, 37.6% steroids, 26% antidepressants, and 2.8% anticonvulsants and tranquilizers. In Zech's study (1995) 15% antidepressants, 13% anticonvulsant and 13% steroids were used for co-analgesia. The choice between these drugs is influenced mainly by the nature of the residual pain; if the residual is clearly flashing, knife-like pain, corticosteroids or anticonvulsant will be preferred with the knowledge that improvement will be likely within 24 hours or less; but if dysaesthesia dominates, antidepressants will be introduced. The tricyclic antidepressants are useful in patients with cancer for variety of reason. In addition to providing a direct analgesic effect, they potentiate the effects of opioid, may provide mood elevation, and help with sleep disturbance (Lucas and Lipman 2002). In our study 301 of 416 (72.35%) patients used antidepressant and anticonvulsants together. If the tricyclic antidepressant alone is not sufficient, another neuropathic pain medication, for example an anticonvulsant, should be added to the tricyclic antidepressants. (Lucas and Lipman 2002).

The drugs used in analgesic ladder therapy have from slight to serious side effects (Drourr et al. 1997, Zylicz and Twycross 1991, Ventafridda et al. 1987). Gastrointestinal system irritation and tendency to bleeding, nephritis and hypersensitivity may occur with non-opiate analgesics (Simmonds 1997). The most common untoward effects of opiates are constipation, nausea-vomiting and sedation (Breivik 2001, Portenoy and Lesage 1999, Simmonds 1997, Zylicz and Twycross 1991). In this study, the common side effects were lower than in others studies (Zech et al. 1995, Ventafridda et al. 1987). This result can be explained by the precautions taken against the expected side effects of pain therapy. One of the reasons is that the majority of our patients used codeine as an opioid. It has lower incidence of opioid-related side effects. However, most of our patients were ambulatory and perhaps they did not report the side effects to us. Although it is not a common side effect, tolerance occurred in one of our patients. This can be prevented by rotation of opioids.

Most cancer pain can be controlled with essential drugs such as paracetamol or acetylsalicylic acid,

codeine and morphine with or without adjuvant taken by mouth according to the WHO analgesic ladder (Breivik 2001, Portenoy and Lesage 1999). However, 5-20 % of patients with cancer pain did not respond to conventional analgesics (Lamer 1994, Charlton 1993). In our study, invasive and/or non-invasive treatment methods were added to the analgesic ladder in 7.5% of patients because of insufficient pain relief at any time during the period of treatment. Zimmerman (1991) reported that invasive methods were used in 15% of patients when conventional method was not effective. Also, Ventafridda et al. (1987) reported that it was necessary to augment the WHO ladder with neurolytic techniques in 29% of their patients. When analgesic ladder therapy fails to control pain or causes excessive side effects patients should be referred to an appropriate specialist or medical center for consideration of other pain relieving techniques (Lamer 1994) but important and serious complications and side effects can happen during invasive therapy. For this reason, experienced physicians must perform invasive interventions in pain therapy departments and the patient must be followed up. Technically simple nerve blocks requiring only basic anatomical knowledge and technical skill but not complex equipment should be realistic alternatives (Breivik 2001). Some patients benefit from neurolytic block of peripheral nerves or sympathetic ganglia, especially celiac ganglion blockade (Chang 2006, Breivik 2001).

The majority of cancer pain patients can be controlled easily with the essential drugs paracetamol or NSAIDs, codeine and morphine taken by mouth using a multidisciplinary approach based on the WHO analgesic ladder. In patients for whom these treatments are ineffective, the indications for alternative treatment methods should be fulfilled, performed by experienced physicians in specialized centers. The best management of pain in cancer patients is only possible with continuous education and respectful collaboration between the physician, the patient and the family.

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