ORIGINAL ARTICLE

Treatment for Neuropathic Pain in Patients with Cancer: Comparative Analysis of Recommendations in National Clinical Practice Guidelines from European Countries

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■ Abstract

Introduction: Neuropathic pain is a common symptom, present in 39% of the patients with cancer pain. Treating this type of pain is challenging, as this patient group is often frail and has comorbidities which increase the risk of side events and hence influences their quality of life. Clinical practice guidelines (CPGs) can be helpful for clinicians,

especially when scientific evidence is uncertain or weak. In this study, we focused on the quality of the review of the literature used in treatment recommendations in the selected European CPGs.

Methods: In a previous study, 9 CPGs from European countries that contained at least one paragraph on treatment for neuropathic pain in cancer were included. Recommendations with their grade (according SIGN 55 classification) and supporting literature (first author, patients' population, year and type of publication) were compared between CPGs.

Results: In all CPGs, amitriptylin was mentioned as the drug of first choice. Six guidelines proposed also gabapentinoids. Only 30 of the 163 citations (18%) were based on studies in patients with cancer. Seven CPGs did not argue the indirect evidence due to extrapolation of study results from non-cancer to patients with cancer.

Conclusion: The majority of guideline development groups extrapolated their results from non-cancer publications to

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formulate recommendations. Consequently, these guidelines fail to address important issues such as altered kinetics and side effect profiles in these patients. We recommend creating specific recommendations by an international expert group for the treatment for neuropathic pain in patients with cancer supported by targeted research in patients with cancer. ■

Key Words: neuralgia, cancer, neuropathic pain, evidence-based medicine, clinical practice guidelines

INTRODUCTION

In Europe, the prevalence of moderate to severe pain in patients with cancer is about 56%.¹ Pain in patients with cancer is often related to a combination of nociceptive and neuropathic mechanisms. In a systematic review of Bennett, the prevalence of neuropathic pain in patients with cancer was found to be 19%. The combination of mixed pain (nociceptive pain) was found to be 39.7%.² Using the World Health Organization (WHO), analgesic ladder for cancer pain relief resolves the nociceptive component in 80% of the treated patients. However, the neuropathic pain component is often more difficult to treat.³ Not all drugs are specifically registered for the treatment for neuropathic pain in patients with cancer in European countries. This implies that most specific drugs used for the treatment for neuropathic pain in patients with cancer are used off-label.⁴ Most clinical research concerning neuropathic pain treatment is performed in patients with diabetic painful neuropathy (DPN) or post-herpetic neuropathy (PHN) and infrequently in patients with neuropathic cancer pain. Patients with cancer suffering from neuropathic pain should be considered different from patients with neuropathic pain in other context for several reasons.⁵ Firstly, approximately 50% of the patients with cancer suffering from neuropathic pain also have nociceptive or visceral pain, in contrast to patients suffering from neuropathic pain in another context.⁶ Secondly, they are more fragile with a potential life-threatening disease. Thirdly, in patients with cancer, the effect size of antiepileptic or antidepressant drug, used in addition to the opioids, is less than that seen in patients with non-cancer neuropathic pain.²

Clinical practice guidelines (CPGs) were created to improve the treatment for a specific condition and are supposed to be based on the latest evidence. Concerning neuropathic pain in patients with cancer, a recent statement of the International Association for the Study of the Pain (IASP) emphasized that the extrapolation of

data from studies of other neuropathic conditions to patients with cancer-induced neuropathic pain is far from straightforward.⁵ In parallel of the evaluation of recommendations on neuropathic pain diagnosis and assessment in patients with cancer,⁷ the aim of this study is to compare recommendations proposed in national CPGs from Europe concerning the treatment for neuropathic pain in patients with cancer and their evidence grading.

METHODS

Study Design

The relation between chosen references, their level of evidence, and the recommendations given in CPGs was systematically studied.

Selection of Guidelines

A European inventory of CPGs was performed with the support of the European Federation of the IASP Chapters (EFIC).⁷ Nine CPGs were included, and this material was used for this study. All CPGs were published between 2006 and 2009^{8–16} from France (1), Italy (2), the Netherlands (2), Norway (2), Spain (1), and the United Kingdom (1). Four were developed under responsibility of a national organization specialized in guideline development.^{9,12,14,15} Five were developed by professional societies (oncology, palliative care, or pain societies).^{8,10,11,13,16} One was developed by an Italian regional health organization (Italy 2).⁸ None of the guidelines were developed solely or specifically for the treatment for neuropathic pain in patients with cancer.

Collection of the Data and Analysis

We developed a procedure to extract recommendations about how to treat neuropathic pain in patients with cancer. Recommendations were defined as “statements that promote or advocate a particular course of action in clinical care”.¹⁷ These treatment recommendations were extracted together with the related references and used as evidence in each CPG. The references were categorized by study design (meta-analysis and systematic review; randomized controlled trial [RCT] with ≥ 60 patients; RCT with < 60 patients; CPG; other) and topic (neuropathic pain, cancer neuropathic pain, cancer pain, acute and chronic pain, and other). Each reference was also considered according to the country of the first author and/or of the work group, journal, and year of

publication. A reference used in at least two CPGs was a shared reference.

Recommendations were analyzed considering drugs proposed to treat neuropathic pain in patients with cancer in each CPG. We focused our analysis on three main drugs: amitriptyline; gabapentin; and pregabalin. For each of these three drugs, we collected positioning in therapeutic strategy (first or second line), start and maximum doses, titration scheme, mentioned side effects and contra-indications, the level of evidence, and the grade of the recommendation, according to the Scottish intercollegiate guidelines network (SIGN) 50 criteria.¹³

Statistical Analysis

Analysis was performed with SPSS 16.0 (IBM, Somers, NY, U.S.A.) using descriptives and frequencies.

RESULTS

Pages Specifically Dedicated to the Treatment for Neuropathic Pain in Patients with Cancer

The nine included CPGs represented 1,480 pages with only 53.5 (4%) pages focusing on the treatment for neuropathic pain in patients with cancer. The sections about the treatment for neuropathic pain in patients with cancer ranged between half a page (Spain) to 37 pages (France) (0.2% to 22%, mostly below 5%).

Characteristics of the References Related to Recommendations Selected in the “Neuropathic Pain in Patients with Cancer” Treatment Section of CPG

Our work collected a total of 163 references related to recommendations selected in the “neuropathic pain in patients with cancer” treatment section of CPGs.

Among these, a majority (116/163: 71%) were about neuropathic pain in non-cancer context. Eighteen (11%) references concerned specifically neuropathic pain treatment in patients with cancer (Table 1). A large majority (80%) of references were related to RCTs and meta-analysis, systematic review, or review. According to SIGN-50, 50 references (31%) could be classified as top evidence level (15 systematic reviews and 35 RCTs with a high number of patients).

Only 30 (18%) of the 163 references were shared between at least two guidelines: 21 shared by two guidelines; four by three guidelines; four by four guidelines; and only one by five guidelines.

References specifically related to neuropathic pain in patients with cancer are presented in Table 2. Among these references specifically related to neuropathic pain in patients with cancer, only four were shared by at least two references.

Treatment for Neuropathic Pain in Patients with Cancer Recommendations and Their Evidence Grading in CPGs

Drugs recommended in selected CPGs are presented in Table 3. Among these, only three classes were recommended by all CPGs: tricyclic antidepressant drugs; $\alpha 2\delta$ agonists; and other anticonvulsant drugs. SNRI antidepressant drugs were recommended by four CPGs (France 2010, Italy 2009, Norway 2007, and Spain). Strong opioids, in combination with co-analgesic, were proposed by five CPGs (France 2010, Italy 2009, the Netherlands 2008-I, Norway 2007, and Spain). However, the Netherlands 2008-II recommended not using them, and three CPGs did not mention them (Italy 2006, U.K., and Norway 2009). Capsaicin plaster was recommended by five guidelines (France 2010, the Netherlands 2008-I, Norway 2007, Spain, and U.K.)

Table 1. Description of CPGs and Characteristics of the References Mentioned in the Section Treatment for Neuropathic Pain in Patients with Cancer

Reference Topic	Number of References	Publication Year	Publication Type					Shared References
			SR+R	RCT $\geq$ 60	RCT < 60	CPG	Other	
Neuropathic pain	116	1969–2007	20	34	49	8	5	22
Cancer neuropathic pain	18	1992–2008	4	1	8	0	5	4
Cancer pain	14	1980–2007	4	0	4	3	3	1
Acute and chronic pain	11	1999–2007	4	0	1	4	2	0
Other	4	2000–2004	2	0	0	0	2	3
Total	163	1969–2008	34	35	62	15	17	30

SR+R, Systematic Review, meta-analysis and review; RCT $\geq$ 60, randomized Controlled Trial with 60 or more patients; RCT < 60, Randomised Controlled Trial with < 60 patients; CPG, Clinical Practice Guideline; Other, cohort study, observational study, case report, local statement; shared references, number of references which are mentioned in at least two guidelines.

Table 2. Neuropathic Pain Treatment in Cancer References in Nine National CPGs from European Countries

Year	Publication Type	Title of the Reference	First Author	Publication	Shared References
2008	RCT, 44*	Amitriptyline in the treatment for chemotherapy-induced neuropathic symptoms.	Kautio	J Pain Symptom Manage	–
2007	RCT, 36	Tramadol in the treatment for neuropathic cancer pain: a double-blind, placebo-controlled study.	Arbaiza	Clin Drug Investig	–
2007	Clinical trial, 65	Gabapentin and an opioid combination vs. opioid alone for the management of neuropathic cancer pain: a randomized open trial.	Keskinbo	J Pain Symptom Manage	+(2 CPGs)
2006	Review	How to use antidepressants and anticonvulsants as adjuvant analgesics in the treatment for neuropathic cancer pain.	McDonald	J Support Oncol	–
2005	Clinical trial, 62	Gabapentin is effective in the treatment for cancer-related neuropathic pain: a prospective, open-label study.	Ross	J Palliat Med	–
2004	RCT, 121	Gabapentin for neuropathic cancer pain: a randomized controlled trial from the Gabapentin Cancer Pain Study Group.	Caraceni	J Clin Oncol	+ (4 CPGs)
2004	Review	Adjuvant analgesics in cancer pain management.	Lussier	Oncologist	–
2003	Systematic review	Ketamine as an adjuvant to opioids for cancer pain.	Bell	J Pain Symptom Manage	–
2002	RCT, 16	Amitriptyline in neuropathic cancer pain in patients on morphine therapy: a randomized placebo-controlled, double-blind crossover study.	Mercadente	Tumori	+(2 CPGs)
2002	RCT, 51	Phase III evaluation of nortriptyline for alleviation of symptoms of cis-platinum induced peripheral neuropathy	Hammack	Pain	–
2002	RCT, 13	Venlafaxine in neuropathic pain following treatment for breast cancer.	Tasmuth	Eur J Pain	–
2001	Case report	Gabapentine for pain control in patients with cancer wound dressing care	Devulder	J Pain Symptom Manage	–
1999	Clinical trial, 593	Assessment and treatment for neuropathic cancer pain following WHO guidelines.	Grond	Pain	–
1999	Clinical trial, 22	Gabapentin as an adjuvant to opioid analgesia for neuropathic cancer pain.	Caraceni	J Pain Symptom Manage	+(2 CPGs)
1997	Review	Neuropathic pain in patients with cancer: mechanisms, syndromes, and clinical controversies. ²²	Martin	J Pain Symptom Manage	–
1992	RCT, 25	Phenytoin as a co-analgesic in cancer pain.	Yajnik	J Pain Symptom Manage	–
1992	RCT, 11	A randomized double-blind crossover trial of intravenous lidocaine in the treatment for neuropathic cancer pain	Bruera	Cancer Treat Rep	–
1989	RCT, 10	Trial of intravenous lidocaine on painful neuropathy in patients with cancer.	Elleman	Clin J Pain	–

RCT, randomized controlled trial; CPGs, clinical practice guidelines.

*Number of patients included in the trial.

and not mentioned in the others. Lidocaine 5% plaster was recommended in three guidelines (France 2010, the Netherlands 2008-I, and Spain) not recommended in two guidelines (Norway 2007 and U.K.) and not mentioned in others. Regarding more invasive therapeutic approaches, only ketamine was recommended after indication confirmation by a pain specialist in four CPGs: Italy 2006, the Netherlands 2008-I, Spain, and U.K. Ketamine was not mentioned by the other CPGs, whereas systemic lidocaine was not recommended in four CPGs (France 2010, Italy 2006 and 2009, the Netherlands 2008-I) or not mentioned in other CPGs.

Focused analysis on amitriptyline, pregabalin, and gabapentin is presented in Table 4. For amitriptyline, evidence level for its recommendation varied from 1++ to four according the SIGN 50 criteria. For pregabalin, evidence level for its recommendation varied also from 1++ to 4. For gabapentin, this level varied from 1++ to 2.

In accordance level of grading varied in the same way for the three drugs. A large majority of CPGs indicated the use rules of drugs but only three CPGs (France 2010, the Netherlands 2008-II and Norway 2009) detailed systematically the side effects and contra-indications of these drugs.

DISCUSSION

In the nine included CPGs on cancer pain or neuropathic pain with at least one chapter on neuropathic pain in patients with cancer, all developed in European countries, 163 references were used to support the given recommendations on neuropathic pain treatment in patients with cancer. Although the proportion of population-specific references was low (11%), it was higher than our previous study on diagnosis and assessment of neuropathic pain in patients with cancer (3%).⁷ Moreover, the mean level of

Table 3. Treatment for Neuropathic Pain in Patients with Cancer According to European National CPGs

Treatment for Neuropathic Pain in Patients with Cancer	France	Italy 2009	Italy 2006	The Netherlands 2008-I	The Netherlands 2008-II	Norway 2009	Norway 2007*	Spain	U.K.*
Paracetamol, NSAIDs,	—	0	0	0	—	0	0	0	0
Weak opioids (ie, dextropropoxyphene, tramadol)	+	0	0	0	—	0	0	0	0
Tricyclic Antidepressant drugs (ie, amitriptyline, imipramine)	+	+	+	+	+	+	+	+	+
SNRI Antidepressant drugs (ie, venlafaxine, duloxetine)	+	+	0	0	0	0	+	+	0
$\alpha 2\delta$ agonists (ie, gabapentine, pregabalin)	+	+	+	+	+	+	+	+	+
Others Anticonvulsant drugs (ie, carbamazepine, valproate of sodium, phenytoine)	+	+	+	+	+	+	+	+	+
Corticosteroides	—	0	0	—	0	+	—	0	0
Opioids (ie, morphine, oxycodone) in combination with coanalgesics	+	+	0	+	—	0	+	+	0
Lidocaine 5% plaster (only in case of local neuropathic pain)	+	0	0	+	0	0	— [†]	+	—
Capsaicin plaster (only in case of local neuropathic pain)	+	0	0	+	0	0	+	+	+
Ketamine	0	0	+ [‡]	+ [‡]	0	0	0	+R	+ [‡]
Lidocaine, mexiletine	—	—	—	—	0	0	0	0	0
Cannabinoides	0	0	0	0	0	0	0	0	—

*The topic of the guideline concerned specifically the treatment for pain in cancer.

[†]No marketing in Norway.

[‡]Consultation with a pain or palliative care specialist (+): should be proposed, (—): should not be proposed, (0): no information. R: refractory neuropathic pain.

evidence of used references was high (44%). Nevertheless, few references were used in at least two CPGs (18%), and no reference was shared by all the CPGs.

All CPGs recommended the use of antidepressant drugs, $\alpha 2\delta$ agonists and others anticonvulsant drugs. Proposal of these drugs in first line treatment is not supported by high evidence level. For example, amitriptyline is the oldest anti-neuropathic drug and well investigated in non-cancer populations,¹⁸ but Mercadante et al.¹⁹ demonstrated the analgesic effects on neuropathic pain of 50 mg of amitriptyline were small and associated with side events in patients with cancer. Similar results were found in another study related to treatment for chemotherapy-induced neuropathic symptoms with amitriptyline.²⁰

We also found diversity in recommendations concerning strong opioids and more invasive approaches such as ketamine. Such second line therapeutic approaches were proposed by some CPGs, whereas they were not mentioned at all in others. This shows a gap between daily practice (wide utilization of ketamine or lidocaine in cancer pain, not only in case of neuropathic pain) and recommendations in part of the CPGs.

Ideally, high quality CPGs should describe adverse events and risks of treatments. In the studied CPGs, these were well described for strong opioids.⁷ However, in the majority of the CPGs, adverse events of antidepressants or anticonvulsants as treatment for neuro-

pathic pain were not mentioned. Up to now, the benefit-risk ratio of these drugs in patients with cancer is unknown.^{19,21} Consequently, we recommend that CPGs mention restrictions when study findings in non-cancer populations are extrapolated to patients with cancer.

Clinical practice guidelines differ in terms of used references, extrapolation techniques, and assigned levels of evidence. The origin and the composition of the guideline development groups seem to have influenced the clinical recommendations,^{22,23} which are based on their clinical experiment and their choice of evidence-based references.

Our results should be interpreted with caution. They are merely based on available information in the CPGs. Only one chapter per CPG concerned neuropathic pain in patients with cancer. These results emphasize the lack of robust references on the treatment for neuropathic pain in cancer conditions. As we limited ourselves to Europe, we were able to develop a detailed study including all European countries. In the future, it would be interesting to include CPGs from other continents.

Recommendations and Perspective

The majority of guideline development groups extrapolated results of studies on non-cancer neuropathic pain to recommendations for patients with cancer. Consequently, these CPGs fail to address important

Table 4. Comparison of Grade of Recommendations and Level of Evidence Proposed for Treating Neuropathic Pain in Cancer Guidelines

	France 2009	Italy 2009	Italy 2006	The Netherlands 2008-1	The Netherlands 2008-2	Norway 2009	Norway 2007	Spain 2008	U.K. 2008
Amitriptyline									
Evidence literature	1	"low"	nm	4	4	1*	nm	1	1 + +
Evidence	A	"weak positive"	A	nm	nm	nm	B	B	A
Start dose	10-25 mg	10-25 mg	10 mg	10-25 mg	10-25 mg	10 mg 2-4 hours before sleep	nm	10-25 mg	nm
Titration scheme	5-25 mg [†]	nm	10 mg/3 days	25 mg/week	25 mg/3-7 days	10 mg/3 days up to 30 mg then 3 weeks stable dose	nm	Slow titration [†]	nm
Maximum dose	75-150 mg	50-75 mg	75 mg	50-150 mg	75 mg	40-50 mg	nm	150 mg	nm
Contra-indications [‡]	+	nm	nm	+	+	+	nm	nm	nm
Side effects [‡]	+	nm	nm	nm	+	+	nm	nm	nm
Pregabalin									
Evidence literature	1	"low"	No treatment option	4	?	1*	nm	1	1 + +
Evidence	A	"weak positive"	option	nm	nm	nm	B	B	A
Start dose	75-150 mg	2 × 25 mg		2 × 75 mg	2 × 75 mg	2 × 25 mg	nm	2 × 25-75 mg	nm
Titration scheme	75 mg [†]	nm		150 mg/2 days	150 mg/2 days	Slowly [†]	nm	50-150 mg/time	nm
Maximum dose	300-600 mg	600 mg		2 × 300 mg	2 × 300 mg	2 × 300 mg	nm	600 mg	nm
Contra-indications [‡]	+	nm		nm	nm		nm	nm	nm
Side effects [‡]	+	nm		nm	+	+	nm	nm	nm
Gabapentin									
Evidence literature	2	"low"	nm	2	2	1*	nm	1+	1 + +
Evidence	A	"weak positive"	A	nm	nm	nm	nm	B	A
Start dose	1 × 100-300 mg	2 × 100 mg	1 × 300 mg	1 × 100-300 mg	1 × 100-300 mg	1 × 300 mg	nm	1 × 300 mg	nm
Titration scheme	100-300 mg [†]	nm	300 mg/day	100-300 mg/day	100-300 mg/day	1 × 300 mg/3 days	nm	1 × 300 mg/day	nm
Maximum dose	1,200-3,600 mg	3,600 mg	3,600 mg	3,600 mg	3,600 mg	3,600 mg	nm	3,600 mg	nm
Contra-indications [‡]	+	nm	+	nm	+	nm	nm	+	nm
Side effects [‡]	+	nm	nm	nm	+	+	nm	nm	nm

*Non-cancer neuropathy.

[†]No further information is given.[‡]+ = mentioned in the CPG, nm = not mentioned in the CPG.

issues such as altered kinetics and side effect profiles in these patients. We recommend creating specific recommendations by an international expert group for the treatment for neuropathic pain in patients with cancer supported by targeted research in patients with cancer. For this purpose, there is a need for research protocols with prospective multicenter and multinational studies in clinical practice comparing different treatment strategies and to publish all studies whether the results reported are positive or negative.

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