REVIEW

Tapentadol in the management of cancer pain: current evidence and future perspectives

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Abstract: Thanks to the progress in early diagnosis and treatment of cancer, the life expectancy of cancer patients has now increased. Patients are, therefore, more likely to experience their individual cancer pain as a chronic pain. As a consequence, long-term treatment of cancer-related pain and oncological therapy-related pain are a major need for all patients and a challenge to all healthcare professionals. Tapentadol is a centrally acting analgesic drug characterized by two synergistic mechanisms of action, since it acts at the μ-opioid receptor (MOR) and inhibits noradrenalin re-uptake (NRI). Therefore, tapentadol has been considered the first of a new class of drugs, MOR-NRI. Tapentadol has been tested in different populations of cancer patients (opioid-naive and -pretreated), such as those with pain of mixed etiology, patients with pain from hematological malignancies and patients experiencing pain conditions due to anticancer treatment. According to available evidence, tapentadol prolonged release was well tolerated and effective in cancer pain patients. In randomized, double-blind and active-controlled trials it proved non-inferior to standard opioids like morphine or oxycodone in the management of moderate-to-severe cancer pain, both in opioid-naive and in opioid-pretreated patients. The good analgesic efficacy may be partly due to the action of tapentadol on neuropathic pain components. Together with the low rate of gastrointestinal adverse effects and the overall favorable safety profile, tapentadol can be considered a good option in cancer pain patients, who can suffer frequently from nausea, vomiting, constipation or other events that further reduce their quality of life.
Keywords: cancer pain, tapentadol, neuropathic pain

Introduction

Pain is highly prevalent in patients with cancer. Up to two-thirds of patients report pain when the disease is at an advanced stage; ~60% of patients on anticancer treatment are affected with pain, and 33% of those on curative therapy complain of this condition as well.[1,2] In approximately two-thirds of patients, cancer pain results from the tumor burden, including metastasis of bones or soft tissues, while in 25% the pain can be attributed to cancer treatment by surgery, radiation or chemotherapy.[1,2] In cancer patients, pain is rated as moderate or severe in ~40% of cases.[2] Pain is associated with interference with daily activities, sleep, mood and social interactions.[1,3] Thanks to the progress in early diagnosis and treatment of cancer, life expectancy of cancer patients has now increased; therefore, patients are more likely to experience their cancer pain as chronic pain. As a consequence, long-term treatment of cancer-related pain is a major need for all patients and a challenge to all healthcare professionals involved in the care of these patients. However, despite existing recommendations to assess and manage pain,[4–8] the

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1553

management of cancer-related pain is often suboptimal and patients are regularly undertreated.[1,8–12] In a recent European survey, 50% of cancer patients believed that their quality of life was not a priority for the healthcare professionals.[9] Cancer patients are often elderly and present a number of comorbidities, making treatment even more challenging.[13]

Cancer pain shares the principal mechanisms of other types of pain. In 60% of cancer patients, the predominant cause of pain was nociceptive, in 20% the dominant component was neuropathic, and the remaining 20% showed a combination of neuropathic and nociceptive pain (so-called mixed pain).[14] Thus, some 40% of cancer patients may suffer from a neuropathic component of their pain. Indeed, bone pain resulting from the metastatic involvement of the skeletal structures can be considered a typical mixed pain.[15,16] Moreover, cancer pain can also result from anticancer therapies.[14,15,17] Finally, cancer patients may have pain independently from their oncological disease, due to other comorbidities.

Tapentadol is an analgesic drug that combines synergistically μ-opioid receptor (MOR) agonism and noradrenalin re-uptake inhibition (NRI) in one molecule. It appears to be unique to date, and therefore it has been classified as the only molecule belonging to a new class of centrally acting analgesics, designated MOR-NRI.[18] Tapentadol appears to be different to classical opioids and may thus be a suitable choice for the treatment of chronic, neuropathic and mixed pain.[19] This relatively new concept has been strengthened and expanded to other drugs (tramadol, buprenorphine, loperamide, cebranopadol) by Raffa and Pergolizzi, who stated that the categorization of all analgesics that have any component of opioid mechanism of action into the same class is anachronistic and misleading.[20,21]

Tapentadol has been tested in different populations of cancer patients, such as those with pain of mixed etiology (opioid-pretreated or -naive patients), with pain from hematological malignancies, and patients experiencing pain due to anticancer treatment.

Based on the authors' experience and the analysis of the available literature, this narrative review presents and discusses the current evidence on the use of tapentadol in the management of cancer pain. The lack of a systematic search for evidence should be taken into account.

Clinical evidence for tapentadol in the treatment of mixed pain in cancer patients

Randomized, placebo-controlled clinical trials in cancer pain patients are a true challenge. Recruitment is hampered by the requirement of a study population of cancer patients that have no other major confounding factors on pain outcome – ie, to find cancer patients with a severe pain, but without relevant comorbidities and interacting drug treatments, which are major recruitment issues. Most suitable patients will likely undergo studies for cancer treatment instead of going into a cancer pain study.

On the other hand, many studies on cancer pain lack an active comparator, and therefore, efficacy and tolerability outcomes are always influenced by comedication and rescue medication. This is a major difference of studies on cancer pain to those on noncancer pain.

With these limitations in mind, the available relevant studies on the use of tapentadol in cancer pain treatment will be discussed.

Randomized, double-blind, active-controlled phase III trials

Most importantly, two multicenter, randomized, double-blind, active-controlled phase III studies have been completed on the use of tapentadol prolonged release (PR) in moderate-to-severe cancer pain: one Asian study was performed in Japan and Korea,[22] and the other trial was a multi-national multicenter study from Europe.[23,24] Table 1 summarizes the key elements of these two pivotal studies.

The Asian study was conducted in 343 patients with a moderate-to-severe pain. They were randomly assigned, in a double-blind fashion, to either tapentadol PR 25–200 mg twice daily or oxycodone controlled release (CR) 5–40 mg twice daily for 4 weeks and were then followed post-treatment for another week.[22] Oral morphine immediate release (IR) 5 mg was allowed as rescue medication for breakthrough pain, without dose limitation. The main goal of the study was to show non-inferiority in efficacy of tapentadol PR vs oxycodone CR. The study populations consisted of opioid-naive Japanese and Korean patients with any type of cancer, mostly within the gastrointestinal and respiratory tract. Over 90% of patients had metastatic cancer; a baseline pain intensity of 4 or beyond on an 11-point numerical rating scale was a prerequisite for inclusion. Overall, tapentadol PR was non-inferior to oxycodone CR: both treatments reduced average pain intensities by 2.6–2.7 points on the 11-point rating scale, respectively. Most importantly, there was no difference between the tapentadol PR-treated group and the patients treated with oxycodone CR in the need for rescue medication, or in the mean total daily rescue doses of oral morphine IR tablets, thus confirming that non-inferiority was not due to a difference in rescue medication use. Moreover,

Table 1 Key elements from randomized controlled clinical trials on tapentadol PR in the treatment of cancer pain

Study	Design	Patients randomized	Tapentadol PR median modal daily dose[a]	Duration study treatment	Efficacy on pain (primary endpoint)	Safety
Imanaka et al[22]	Randomized, double-blind, active-controlled (oxycodone CR), multicenter phase III study. Rescue medication: morphine IR 5 mg as needed	Asia: 343 opioid-naive patients with moderate-to-severe, chronic malignant tumor-related pain	TDD: 50.0 mg Allowed dose range: 25–200 mg twice daily	Median: 28 days	Mean difference in the change in pain intensity (baseline vs 3 last days of treatment, tapendatol PR vs oxycodone CR): –0.06 (95% CI: –0.506–0.383)[b]	Patients with at least one TEAE: Tapentadol PR 87.5% vs oxycodone CR 90.1% Patients with at least one gastrointestinal TEAE: Tapentadol PR 55.4% vs oxycodone CR 67.4%
Kress et al[23]	Randomized withdrawal, parallel group, active (morphine CR) and placebo-controlled, double-blind, multicenter phase III study. Rescue medication: Morphine IR 10 mg as needed	Europe: 496 opioid-pretreated or opioid-naive patients with moderate-to-severe, chronic malignant tumor-related pain. 2/3 with neuropathic pain component	TDD: 300 mg Allowed dose range: 100–250 mg twice daily	Median: 14 days of titration period, followed by re-randomization for another 28-day maintenance period	Responder rate at the end of titration: tapentadol PR 76.0%, morphine CR 83.0% (P=0.001 for non-inferiority) Adjusted responder rate during maintenance (primary endpoint): 64.3% with tapentadol, 47.1% with placebo (P=0.02)	During titration: incidence of TEAEs: 50.0% with tapentadol, 63.9% with morphine. Incidence of nausea, vomiting, and dry mouth significantly lower with tapentadol PR than with morphine CR (P<0.0039) During maintenance: incidences of TEAEs were 56.3% with placebo, 62.3% (66/106) with tapentadol PR, and 62.4% (68/109) with morphine CR

Note: [a]Median modal daily dose = most frequently used daily dose. [b]Non-inferiority.
Abbreviations: CR, controlled release; IR, immediate release; PR, prolonged release; TDD, total daily dose; TEAE, treatment-emergent adverse events.

tapentadol PR was at least as effective in cancer-related pain relief as oxycodone CR in terms of response (≥30 or ≥50% decrease in pain intensity compared with baseline). Lastly, the Patient Global Impression of Change also showed that tapentadol was at least as good as oxycodone in providing sufficient pain relief: 58.7% of the patients treated with tapentadol PR reported a much improved or improved pain vs 50.4% in the oxycodone CR-treated group. Remarkably, a significantly lower rate of constipation was reported with tapentadol compared with oxycodone. Overall, the Asian trial in opioid-naive patients with moderate-to-severe chronic malignant tumor-related pain revealed an effective pain relief

at tapentadol PR dosages of 25–200 mg twice daily, and non-inferiority to oxycodone CR at dosages between 5 and 40 mg twice daily.

The European phase III trial evaluated the efficacy and tolerability of tapentadol PR compared with placebo and morphine CR for managing moderate-to-severe chronic malignant tumor-related pain.[23] Differing from the Asian study, the European trial investigated the effect of tapentadol PR in cancer patients with chronic, moderate-to-severe, malignant tumor-related pain, who were either opioid-naive or opioid-pretreated with morphine or another opioid drug up to a maximum dose of 160 mg morphine equivalent per

day, and who were dissatisfied with their prior analgesic medication. This was obviously a different patient population compared with the purely opioid-naive patients recruited in the Asian study. Moreover, the design of the European study was much more complex than the design of the Asian study. Patients with a cancer-related pain of 5 or more on the 11-point numerical rating scale (NRS) were randomly assigned, in a 2:1 ratio, to either tapentadol PR titration up to 100–250 mg twice daily or to a morphine CR titration ranging from 40 up to 100 mg twice daily. This titration period took 2 weeks and involved 496 patients. Thereafter, the individuals were again randomized: those who were on tapentadol during titration were randomized 1:1 to continue with tapentadol at the last dose or to be withdrawn from tapentadol and start receiving placebo. In order not to unblind the morphine sulfate-treated patient group, they were also pseudo-randomized but continued, in a blinded fashion, on their last morphine CR medication reached at the end of the titration period. This second trial period, with three arms including the enriched-withdrawal design for the tapentadol PR group, is referred to as the maintenance period in the following and lasted another 28 days.

The majority of evaluated patients suffered from breast cancer, cancer of the respiratory tract or prostate cancer; 80% presented metastases, mainly of bones or lymph nodes. One-third of the patients in each arm was >56 years of age, gender and body mass index did not show any differences between the groups. In both groups, two-thirds of the patients suffered also from neuropathic pain, whereas neuropathic pain was not recorded in the Asian study.

The primary efficacy endpoint was the rate of responders at the end of the 4-week maintenance period. A responder was defined as a patient who completed the 28 days of maintenance and showed a mean pain intensity score <5 on NRS and used only 20 mg or less of rescue morphine medication per day on average. There was a significant difference in favor of a higher responder rate in the tapentadol PR group compared with placebo. Therefore, tapentadol PR proved effective in moderate-to-severe cancer pain, although the comparator placebo group had also access to morphine IR rescue medication.

During the totally blinded 2-week titration period, patients taking tapentadol PR could directly be compared with those taking morphine CR for titration. At the end of the titration period, responders were again defined as those patients who completed the titration phase, showing a mean pain intensity score <5 and having used only 20 mg per day or less of additional morphine IR rescue medication. Again,

clear non-inferiority of tapentadol PR vs morphine CR could be shown at a dose ratio of 2.5:1 during the titration phase, and the study endpoint was reached. This dose ratio was also reconfirmed, when the medium modal daily doses of tapentadol PR and morphine CR were compared during the titration (300 mg for tapentadol PR vs 120 mg median modal daily dose for morphine CR).

When only those patients with a neuropathic pain component were analyzed, there was a tendency of higher response rate to tapentadol, which did not reach statistical significance in this relatively small sample, however.

Similar to the Asian study results, significantly lower percentages of patients with any treatment-emergent adverse events were seen in the tapentadol PR compared with the morphine CR group. In particular, 29.6% the gastrointestinal disorders were significantly lower under tapentadol PR compared with 46.8% in the morphine CR group. Similarly, fewer side effects in the nervous system and fewer general disorders were reported under tapentadol, but this did not reach statistical significance.

A separately published post hoc analysis of the European trial investigated the efficacy and tolerability of tapentadol PR in patients who were dissatisfied with their previous tramadol treatment and who had a pain intensity ≥5 on NRS before converting to tapentadol PR (n=129).[24] Results for this subgroup were compared with results for all patients who received tapentadol PR during titration (n=338). The responder rates were slightly better for the tramadol/tapentadol PR subgroup vs the overall tapentadol PR group (69.8 vs 63.9%). Tolerability profiles were comparable. Overall, these findings suggest that in patients with cancer pain switching from tramadol to tapentadol is feasible, well tolerated and likely associated with improved analgesic efficacy.

Open-label or observational tapentadol studies

In a separate study from Japan, Imanaka et al[25] evaluated the conversion to oral tapentadol PR (50–250 mg twice daily) from previous around-the-clock strong opioid therapy in patients with moderate-to-severe, well-controlled, tumor-related cancer pain. This randomized, open-label, phase III study consisted of a 1- to 2-week screening period (still on the previous opioid) followed by an 8-week, open-label period. Eligible patients were randomly assigned to receive twice-daily treatment with tapentadol PR (100–500 mg/day) or morphine CR (20–140 mg/day). The primary endpoint was the proportion of patients who maintained pain control (change from baseline in mean pain intensity on NRS <1.5

for three consecutive days and no more than two doses of rescue medication/day for three consecutive days) during the first week of open-label treatment. In the tapentadol PR group (n=50), 84.0% of patients kept pain control during week 1, compared with 98% with morphine. Tapentadol PR was associated with a lower incidence of gastrointestinal treatment-emergent adverse events than morphine (38.0% vs 54.0%), including constipation (12.0% vs 20.0%) and vomiting (6.0% vs 26.0%).

Mercadante et al[26] conducted a 4-week prospective study in 50 opioid-naive cancer patients with moderate-to-severe pain; each patient received twice-daily doses of tapentadol PR 50 mg, and doses were then titrated according to clinical response. In total, 39 patients completed the study. Pain intensity significantly decreased from baseline starting from week 1, and quality of life improved over the study period. Tapentadol escalation indexes were low and no correlation with age, gender and pain mechanisms was reported. Importantly, no worsening of clinical status was documented, and tapentadol was also well tolerated in patients previously on NSAIDs/paracetamol.

An open-label, prospective, noninterventional study in 123 cancer pain patients, 42.3% of whom were on strong opioids prior to the initiation of tapentadol treatment, documented a significantly lower mean pain intensity on NRS by the end of the 3-month observation period after the switch to tapentadol PR treatment. This finding was consistent for "lowest pain intensity" as well as for "average pain intensity" and "highest pain intensity." Patients were very satisfied with the tapentadol treatment of their cancer-related pain under these real-life conditions: the majority of patients very much improved or at least improved in their general condition after the switch to tapentadol.[27]

Finally, Cascella et al[28] have recently published the results of an observational prospective study in 80 cancer patients, either opioid-naive or pretreated. In total, 70 out of 80 patients (88%) were responders. Compared to baseline, a decrease in pain intensity was reported at all assessments, till day 70 of treatment. Only two patients (2.5%) left the study for tapentadol-related adverse events. A significant improvement in quality of life was noticeable after 30–40 days, and the majority of patients were "satisfied," "very satisfied," or "extremely satisfied" with treatment.

In clinical practice, it has been observed that switching a patient from a high dose of a strong μ-opioid to an equi-analgesic dose of tapentadol PR may lead to features of mild acute opioid withdrawal, thus confirming that tapentadol cannot simply be considered another opioid.[19] This issue has been investigated in two studies by Mercadante et al;[29,30]

the overall results show that, for average doses, the switch is feasible and well tolerated, also in opioid-pretreated patients.

Tapentadol in patients with pain related to hematological malignancies

Myeloma bone disease is a major complication of multiple myeloma associated with severe pain. Coluzzi et al[31] prospectively evaluated the efficacy and tolerability of tapentadol PR in the management of 25 patients with myeloma bone disease, who were opioid-naive with moderate-to-severe pain. Patients initially received tapentadol PR 50 mg twice daily, and doses were titrated according to clinical needs. In total, 22 patients completed the study. Pain intensity significantly decreased from baseline as early as at week 1 ($P<0.01$); this improvement in pain intensity was paralleled by improved quality of life, as assessed by the SF-36 scale. Tapentadol PR was also associated with a reduction in DN4 (Douleur Neuropathique 4) mean values ($P<0.01$), which can be useful for distinguishing neuropathic from nociceptive pain.[32] During tapentadol therapy, the number of patients showing a neuropathic component of pain (DN4 ≥4) significantly decreased ($P<0.01$). At week 8, all patients were negative for neuropathic pain by means of the DN4 score. Tapentadol PR was well tolerated, and the use of other analgesics reduced over the study period. Overall, the authors of the study concluded that tapentadol PR can be considered a first-choice opioid in cancer patients suffering from mixed pain with a neuropathic component.

In a retrospective study specifically conducted in 36 challenging (NRS≥5) patients with hematological malignancies and uncontrolled pain, Brunetti et al[33] explored the safety and efficacy of tapentadol PR. Overall, a remarkable (–7 points out of 11) reduction of pain intensity was reported, without any relevant adverse event.

Tapentadol in cancer treatment-related pain

Mucositis is a frequent and painful side effect of chemotherapy and radiotherapy. Mazzola et al[34] evaluated the effectiveness and tolerability profile of tapentadol PR in a cohort study of 30 opioid-naive head and neck cancer patients with background pain due to painful mucositis during intensity-modulated radiation therapy with or without cisplatin with either definitive or adjuvant intent. Tapentadol PR 50 mg twice daily was given at pain onset; this dosage could be increased according to clinical needs. The observation period

was 90 days from the start of antineoplastic treatment: 22 days after the initiation of antineoplastic treatment, tapentadol PR was administered to 25% of patients. This percentage increased to 50% after 39 days and to 75% after 43 days. A reduction by 30% of pain intensity in 26 patients (86.7%), and a reduction of 50% in 23 patients (76.7 %) were reported.

Many chemotherapeutic agents can induce peripheral neuropathy (CIPN), and patients with CIPN often experience neuropathic pain. Galiè et al[35] conducted a prospective, open-label study to evaluate the efficacy and tolerability of tapentadol PR in patients with CIPN secondary to taxane- and/or platinum-based regimens. After 3-month treatment with tapentadol, 22 patients were evaluated, with 19 (86%) of them showing a response (NRS reduction ≥3 vs baseline). Tapentadol also reduced NRS and DN4 values from baseline to the last visit, and an improvement of their health status as measured by the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 (EORTC-QLQ-C30) was reported.

Conclusions

In all clinical studies with cancer pain patients, tapentadol PR was well tolerated and provided adequate analgesia, which was at least non-inferior to the standard opioids morphine CR or oxycodone CR. Based on the high level of evidence derived from two independent randomized, double-blind, active-controlled phase III trials (one of which was larger than any trial on opioids in this setting), together with the admittedly weaker evidence from various open-label or observational clinical studies, tapentadol PR can be considered a universal, strong, centrally acting analgesic drug for the management of moderate-to-severe cancer pain, both in opioid-naive and already opioid-pretreated patients. Its good analgesic efficacy seems to be due, at least in part, to the inherent synergistic mechanisms of tapentadol acting also on neuropathic components of cancer pain.

Remarkably, a Cochrane review, published in 2015, revealed that tapentadol appeared at least as effective as morphine or oxycodone in pain relief for cancer patients.[36] This finding might have immediate clinical relevance given the mounting importance of opioid rotation for pain therapy in oncological patients: tapentadol can represent an alternative within this approach.[37] Moreover, it is worth noticing that many cancer patients do show hepatic decompensation, thus limiting the use of tramadol.[38]

Preliminary evidence indicates that tapentadol PR might be also a suitable therapy for pain associated with oncological treatments, such as intensity-modulated radiotherapy or chemotherapy.

The reduced occurrence of gastrointestinal adverse effects and the overall favorable safety profile of tapentadol may be an advantage in cancer pain patients, who frequently – and because of multiple causes – suffer from nausea or vomiting, constipation or other events that further reduce their already poor quality of life. The low potential of tapentadol for undergoing drug–drug interactions is another important advantage in the setting of cancer patients under extensive pharmacological therapy. For all these reasons, tapentadol can be considered a suitable option for supportive care in those vulnerable cancer patients, who are particularly prone to experience gastrointestinal adverse events.

Key points

- Pain in cancer patients is often undertreated and can have both nociceptive and neuropathic components.
- Traditional opioids may not be best choice in all cancer patients with pain, since they do not always act on the neuropathic components of their pain, and are associated with a higher risk of adverse events and drug–drug interactions compared with tapentadol.
- In cancer pain patients, tapentadol PR was well tolerated and effective, and therefore can be considered a universal analgesic to be used for the management of moderate-to-severe cancer pain in opioid-naive and opioid-pretreated patients.
- The good analgesic efficacy may be due, at least in part, to the action of tapentadol on neuropathic components of pain.
- The lower rate of gastrointestinal adverse effects and the overall favorable safety profile of tapentadol compared to other opioid analgesics may be of advantage in cancer patients frequently suffering from nausea, vomiting, constipation or other events that further reduce their quality of life.
- The low potential for drug–drug interactions is another favorable property of tapentadol in cancer patients under extensive pharmacological therapy.

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Disclosure

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