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ORIGINAL ARTICLE

Quality of analgesic treatment in patients with advanced prostate cancer: do we do a better job now? The Swiss Group for Clinical Cancer Research (SAKK) experience

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Abstract
Goals of work The aim of this study was to evaluate pain intensity and the application of the WHO guidelines for cancer pain treatment in patients with prostate cancer treated at Swiss cancer centers.
Materials and methods We analyzed a series of five multicenter phase II clinical trials which examined the palliative effect of different chemotherapies in patients with advanced hormone-refractory prostate carcinoma. Of 170 patients, 1,018 visits were evaluable for our purpose, including ratings of pain intensity by patients and prescribed analgesics.
Main results No or mild pain was indicated by patients in 36 to 55% of the visits, more than mild pain in 30 to 46%. In 21% of the visits, the WHO pain treatment criteria (treatment according to one of the three steps; oral, rectal or transdermal application of the main dose; administration on a regular schedule) were fulfilled, and the Cleeland index was positive according to all recommendations. In 6% of the visits, neither the WHO criteria were fulfilled nor was the Cleeland index positive. This indicates insufficient pain treatment not following the WHO guidelines and that the prescribed analgesics were not sufficiently potent for the rated pain intensity.
Conclusions In this selective Swiss sample, the standard of analgesic treatment is high. However, there is still scope for improvement. This cannot solely be solved by improving the knowledge of the physicians. Programs to change the patients' attitude towards cancer pain, training to improve the physicians' communication skills, and institutional changes may be promising strategies.

Keywords Prostate cancer · Pain · Analgesic treatment · WHO guidelines · Pain management index

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Introduction

Prostate cancer is the most commonly diagnosed male cancer and is likely to become even more important mainly because of the increasing number of elderly people in the population and probably because of improved surveillance and early diagnosis [17]. With a 5-year survival rate of 75%, it is one of the cancers with a favorable prognosis. Nevertheless, prostate cancer in advanced stages remains a disease with few therapeutic options. In primarily localized

disease, metastases develop in 30 to 50% [12, 14, 29] and are already present at the time of diagnosis in 15 to 25% of patients. Metastatic prostate cancer involves many organs, but the skeleton is most frequently involved with 84% or more of distant metastases. Pain is the primary symptom of metastatic disease, occurring in 50 to 75% of patients [3, 9, 16] or even more [5]. Severe pain does not only cause enormous suffering, it also leads to impairment in the activities of daily living, to psychological, familial, and professional dysfunction and disturbance of sleep, appetite, and vitality [11, 26]. Thus, analgesic treatment is a major aim in these patients.

In 1986, the World Health Organization (WHO) started a worldwide campaign for cancer pain relief, proposing guidelines on effective use of drugs to treat cancer pain, based on ample clinical and empirical experience. The proposed three-step treatment is simple and efficacious [27]. Are these guidelines really applied in clinical routine? Former investigations showed that 40 to 50% of patients with cancer pain receive insufficient analgesic therapy despite these guidelines [2, 7, 26, 28].

In this study, we retrospectively investigated the situation in Switzerland by analyzing a series of five multicenter phase II clinical trials which examined the palliative effect of different chemotherapies in patients with advanced hormone-refractory prostate carcinoma [15, 20–22, 24]. Only patients treated at major Swiss cancer centers, where optimal treatment can be expected, were included in this study. Their pain intensity and individual analgesic treatment were recorded from enrollment into the trial until chemotherapy was stopped (e.g., due to tumor progression, severe toxicity). In contrast, most other reports on analgesic treatment in cancer patients have been based on cross-sectional analyses [4, 25] or examined shorter periods, e.g., as long as the patients were hospitalized [1, 2, 6, 18, 28].

Materials and methods

The SAKK trials

From 1991 to 2001, the Swiss Group for Clinical Cancer Research (SAKK) has conducted five phase II trials of various chemotherapeutics in patients with hormone-refractory advanced prostate cancer within the framework of a master protocol [15, 20–22, 24]. For the evaluation of palliative benefit, pain intensity and pain treatment were recorded in addition to clinical endpoints. All patients received a chemotherapy according to the corresponding trial protocol. Analgesic therapy was prescribed individually.

The inclusion criteria were similar in all five trials: histologically or cytologically proven prostate cancer, advanced disease with metastases, documented progression under previous endocrine therapy, life expectancy of at least 3 months, sufficient bone marrow reserve, adequate liver and renal function, continuation of LH-RH analogues; antiandrogens stopped at least 1 month before enrollment [20–22] or before chemotherapy was given [24], radiotherapy stopped at least 3 [20] or 4 weeks [15, 21, 22, 24] before enrollment, no previous chemotherapy (except in the first trial [15]).

First trial (SAKK 08/91; 1991–1993)

Carboplatin was administered [15]. Inclusion criteria not mentioned above: WHO performance status ≤3 (range 0–4), measurable tumor lesions or WHO pain index ≥2 [range 0 (no pain)–4]. There was no upper age limit. Four of the 28 patients had previous chemotherapy. Endocrine therapy had to be continued during the trial treatment. Treatment was stopped if there was a subjective or objective assessment of tumor progression (i.e., treatment failure), unexpected severe toxicities, refusal by the patient, or any other serious medical complication.

Second trial (SAKK 08/93; 1993–1995)

Oral Idarubicin was administered [24]. Patients older than 80 years or with severe heart disease were excluded. A maximum of 11 cycles was allowed. Treatment was stopped in case of patient refusal, deterioration of renal or hepatic function, toxicities of grade 3 or 4 according to WHO criteria, or progression of disease.

Third trial (SAKK 08/95; 1995-1997)

Gemcitabine was administered [20]. Upper age limit was 80 years. WHO performance status had to be ≤2 and prostate-specific antigen (PSA) level at least three times the upper normal level. Treatment was stopped after ten cycles or in case of tumor progression (according to PSA levels, progression of known lesions or appearance of new metastases on X-rays or bone scans), unexpected severe toxicities, refusal by patient or any other serious medical complication.

Fourth trial (SAKK 08/97; 1997–1999)

Vinorelbine was administered [22]. Upper age limit was 85 years. Patients with known leptomeningeal or brain metastases were excluded. WHO performance status had to be ≤2 and PSA level at least three times the upper normal level. A maximum of 12 cycles was administered. Treatment was stopped in case of patient refusal, unacceptable toxicity or tumor progression (new lesions, increase of measurable lesions or PSA progression).

Fifth trial (SAKK 08/00; 2000–2001)

Capecitabine was administered [21]. Upper age limit was 85 years. Patients with known brain metastases were excluded. WHO performance status had to be ≤2 and PSA level ≥5 ng/ml. A maximum of eight cycles was administered. Treatment was stopped when there was PSA progression or documented clinical progression.

Assessment of pain intensity

Pain intensity was one of several quality of life domains assessed by the patients based on the EORTC questionnaire (EORTC QLQ-C30). The scale had a range from 1 to 4 ("not at all", "a little", "quite a bit", "very much"). The time frame was related to the past week. This assessment was made on each visit to the hospital (at baseline, on day 8 of the first chemotherapy cycle, and day 1 of each following cycle) until treatment failure.

Assessment of pain treatment

For every visit, we investigated whether the analgesic treatment was administered according to three criteria of the WHO guidelines: Three-step treatment (starting with an NSAID or paracetamol, adding a weak opioid such as tramadol in the second step, and a strong opioid such as morphine in the third step); mainly oral, rectal, or transdermal administration; regular administration "around the clock", i.e., at fixed time intervals. The application according to the drugs' pharmacokinetics could not be evaluated. Based on clinical experience, our primary hypothesis was that the WHO analgesic ladder was not followed. In particular, we hypothesized that the opioids were prescribed without addition of paracetamol or NSAID.

For a summary evaluation, we analyzed for all visits whether or not the patients were treated according to the WHO pain treatment criteria, as defined above (yes/no). "Yes" was assigned if all of the three WHO pain treatment criteria were fulfilled.

In addition, for purpose of consistency, we calculated the Cleeland pain management index for every visit [4]. This index compares the most potent analgesic prescribed for that patient with the patient's reported level of pain. Four levels of analgesic therapy are defined: 0, no analgesic drug; 1, a non-opioid (e.g., a NSAID); 2, a weak opioid; 3, a strong opioid (e.g., morphine). In addition, four levels of pain are defined, in correspondence with our patient-rated pain scale: 0, absence of pain; 1, mild pain; 2, moderate pain; and 3, severe pain. The pain management index is calculated by subtracting the pain level from the analgesic level and ranges from −3 (a patient with severe pain receiving no analgesic drugs) to +3 (a patient reporting no pain receiving morphine or an equivalent). Negative scores are considered to indicate inadequate orders for analgesic drugs, and scores of 0 or higher are considered to be a conservative indicator of acceptable treatment.

Statistical analysis

Pain intensity and treatment were presented by descriptive statistics or frequency counts. All analyses were carried out for the whole dataset and for two subsets stratified by patient-rated pain intensity: visits with less pain (EORTC pain score=0 "not at all" or=1 "a little") vs visits with substantial pain (EORTC pain score=3 "quite a bit" or=4 "very much"). This grouping is consistent with the results by Serlin et al. [25] who showed a consistent pattern of pain interference as a function of pain severity.

Results

Sample description and patient characteristics

Overall, 170 patients and 1,018 visits were evaluable for our purpose. The number of visits varied from 132 to 252 per trial. Across all trials, the median number of visits per patient was between six (minimum/maximum over all trials: 2/15).

Pain treatment documented by the physician was available for all visits. However, some of the items were not answered or the response was considered invalid: WHO step 2% (n=22), administration route 5% (n=49), administration schedule 5% (n=51), and physician-rated pain 3% (n=28). Patient-rated pain was available for 85% of the visits (n=870). Fulfillment of WHO pain treatment criteria could not be calculated for visits in which patients received no analgesics (271 visits or 27% of all visits).

The patients' characteristics at baseline are summarized in Tables 1 and 2. Because of the similar inclusion criteria, the trial samples are homogeneous: most of the patients had bone metastases, a performance status of 0 or 1 (exception: first trial); in all trials, the median age was between 68 and 72 years. The patient-rated pain intensity at baseline varied from 41% of patients indicating more than mild pain [22] up to 71% [15].

Pain intensity

Overall, in 262 visits (26%), the patients indicated no pain, in 242 visits (24%) "a little" pain, in 248 visits (24%) "quite a bit" pain and in 125 visits (12%) "very much" pain, corresponding to 373 visits (37%) with more than mild pain. For the individual trials, no or mild pain was indicated in 36

Table 1 Patient characteristics at baseline

SAKK[a] Trial no.	Number of patients	Previous radiotherapy Yes/No	Bone metastases Yes/No	Performance status 0-1/2-3	Median age (range) years
08/91	28	14 (50%)/14 (50%)	24 (86%)/4 (14%)	11 (39%)/17 (61%)	68 (50–82)
08/93	30	10 (33%)/20 (67%)	29 (97%)/1 (3%)	24 (80%)/6 (20%)	72 (52–80)
08/95	43	19 (44%)/24 (56%)	41 (98%)/1 (2%)	31 (72%)/12 (28%)	69 (50–80)
08/97	44	23 (52%)/21 (48%)	38 (86%)/6 (14%)	36 (82%)/8 (18%)	71 (45–83)
08/00	25	12 (48%)/13 (52%)	24 (96%)/1 (4%)	21 (84%)/4 (16%)	70 (45–84)
Total	170	78 (46%)/92 (54%)	156 (92%)/13 (8%)	123 (72%)/47 (28%)	70 (45–84)

[a] Schweizerische Arbeitsgemeinschaft für klinische Krebsforschung (Swiss Group for Clinical Cancer Research)

to 55% of the visits, more than mild pain was indicated in 30 to 46%.

Treatment according to the WHO steps

In 539 visits (53%), the analgesics were administered according to the three WHO steps: 25% WHO step I with NSAID and/or paracetamol, 10% WHO step II with weak opioids, and 18% WHO step III with strong opioids. In 29% of the 539 visits, adjuvant drugs were added to classical analgesics. In further 159 visits (16%), weak or strong opioids were prescribed without NSAID/Paracetamol. In 27 visits (3%), only adjuvant drugs were prescribed. Table 3 shows the analgesic treatment of the two subsets (no or mild pain, more than mild pain). Overall, opioids were prescribed in 439 visits (43%) and in 58% of visits of patients indicating more than mild pain. In 64% of these 439 visits, the opioids were combined with paracetamol and/or NSAID.

Administration route

In 657 visits (65%), at least one basic medication was administered orally, in five visits (0.5%) rectally, in 31 visits (3%) in a transdermal system, in three visits (0.3%) subcutaneously, and in 2 visits (0.2%) peridurally, never intravenously. The only relevant change between the trials was an increase in the use of transdermal systems from 0% in the first to 11% in the most recent trial. In patients with more than mild pain, there were more oral analgesics (84% of visits) and more transdermal systems (5%) prescribed than in patients with no or mild pain (50 and <1%, respectively).

Administration schedule

In 520 visits (51%), the analgesics were prescribed on a regular schedule (by the clock). In 174 visits (17%), the analgesics were only given on demand. Comparing between trials, the analgesics were prescribed most frequently on a regular schedule in the first trial (in 58% of visits) and least frequently in the fourth trial (42% of visits). In patients indicating more than mild pain, analgesics were prescribed more frequently on a regular schedule (71% of visits) compared to patients with no or mild pain (35% of visits).

Summary evaluation

Treatment according to WHO criteria Overall, analgesic treatment was sufficient according to the three WHO pain treatment criteria (treatment according to one of the three steps; oral, rectal, or transdermal application of the main dose; administration on a regular schedule) in 345 visits (34%). In further 349 visits (34%), at least one criterion was not fulfilled. In patients indicating more than mild pain, we observed a higher proportion of treatments according to the WHO criteria (50% of visits) compared to patients with no or mild pain (22% of visits). In 39% of the visits of patients with more than mild pain, at least one criterion was not fulfilled.

Table 2 Patient-rated pain intensity at baseline

SAKK[a] Trial no.	No pain	Mild pain	Moderate pain	Severe pain	Data not available
08/91	3 (11%)	3 (11%)	8 (29%)	12 (43%)	2 (7%)
08/93	6 (20%)	4 (13%)	11 (37%)	8 (27%)	1 (3%)
08/95	5 (12%)	14 (33%)	16 (37%)	6 (14%)	2 (5%)
08/97	13 (30%)	12 (27%)	11 (25%)	7 (16%)	1 (2%)
08/00	2 (8%)	10 (40%)	5 (20%)	7 (28%)	1 (4%)
Total	29 (17%)	43 (25%)	51 (30%)	40 (24%)	7 (4%)

[a] Schweizerische Arbeitsgemeinschaft für klinische Krebsforschung (Swiss Group for Clinical Cancer Research)

Table 3 Patient-rated pain intensity and treatment steps according to the WHO steps

Treatment steps	No pain or mild pain	Moderate pain or severe pain	Data not available	Total
No analgesics	217 (43%)	26 (7%)	28 (20%)	271 (27%)
Step 1	110 (22%)	119 (32%)	30 (21%)	259 (25%)
Step 2	29 (6%)	54 (14%)	14 (10%)	97 (10%)
Step 3	54 (11%)	101 (27%)	28 (20%)	183 (18%)
Treatment with weak or strong opioids, no NSAID[a]/Paracetamol	66 (13%)	63 (17%)	30 (21%)	159 (16%)
Only adjuvant drugs	24 (5%)	1 (<1%)	2 (1%)	27 (3%)
Not defined/missing	4 (<1%)	9 (2%)	8 (6%)	21 (2%)
Total	504	373	140	1017

[a] Non-steroidal anti-inflammatory drugs

Treatment according to Cleeland index Overall, in 636 visits (63%), there was a Cleeland index ≥0, indicating that the prescribed class of analgesics was adequate for the reported pain intensity. In 231 visits (23%), the Cleeland index was <0, indicating that the prescribed analgesics were inadequate for the reported pain intensity. In patients indicating no or mild pain, the Cleeland index was ≥0 in 436 visits (87%) and <0 in 58 visits (12%). In patients indicating more than mild pain, the Cleeland index was ≥0 in 190 visits (51%) and <0 in 170 visits (46%).

Insufficient pain treatment according to both WHO criteria and Cleeland Index Overall, in 215 visits (21%), the three WHO pain treatment criteria were fulfilled, and the Cleeland index was ≥0, indicating adequate pain treatment according to both requirements. In 59 visits (6%), neither the WHO criteria were fulfilled nor was there a Cleeland index ≥0 pointing to insufficient pain treatment: It did not follow the WHO criteria, and the prescribed analgesics were not sufficiently potent for the indicated pain intensity. In 319 visits, one of these two requirements was not fulfilled (WHO criteria not fulfilled in 233 visits or 23%, Cleeland index <0 in 86 visits or 8%).

Discussion

We examined the quality of pain treatment in Swiss cancer centers. The study is based on an analysis of five multicenter phase II clinical trials on the palliative effect of different chemotherapies in patients with advanced hormone-refractory prostate carcinoma. In these patients, pain is a common symptom, and the major treatment goal is sufficient pain control. We examined only patients who were treated at cancer centers. In such a selective sample, we expected an optimal pain treatment.

It is difficult to judge the quality of pain treatment because there is insufficient evidence from controlled trials concerning adherence to the WHO guidelines [13]. Given that the examined trials were designed for another, although related purpose (i.e., palliative benefit by chemotherapy), such a judgment would be even more difficult. However, it was possible to investigate formal aspects which affect the quality of the analgesic treatment. Our findings highlight key aspects of cancer pain and its treatment in Switzerland in the nineties.

During the chemotherapy period, there was a decrease in patient-rated pain intensity: 50% of the patients indicated no or mild pain on chemotherapy compared to 42% at baseline; 37% of patients indicated more than mild pain on chemotherapy compared to 54% at baseline. It is difficult to judge if these lower pain ratings during the chemotherapy period compared to the baseline are due to a better pain management at the cancer centers or to the

Table 4 Shortcomings

Shortcomings
NSAID[a] and/or paracetamol is prescribed in patients with substantial pain instead of opioids
The dose of opioids is not adjusted when not sufficient
Opioids are not combined with NSAID or paracetamol
Opioids as basic medication, but the rescue medication for breakthrough pain is an NSAID or paracetamol instead of an opioid
Rescue medication for breakthrough pain is a retard formulation instead of an immediately effective preparation
The analgesic medication is reduced too rapidly, when pain is treated successfully
Treatment with different drugs at one step instead of one medication for each step
Different drugs for rescue medication instead of a sufficient basic medication

[a] Non-steroidal anti-inflammatory drugs

effect of the administered chemotherapies. Their palliative benefit has been published elsewhere [15, 20–22, 24]. These figures are fairly consistent with those found in other reports on patients with prostate cancer: In the study of Calais da Silva et al. [3], 30% of patients at baseline and up to 59% during the study indicated no pain, and only 28% of patients in the study by Curran et al. [5] indicated quite a bit or very much pain. Fosså et al. [9] described a higher percentage: 55% of patients indicated quite a bit or very much pain at baseline. Pollen and Schmidt [23] found an even higher percentage of cancer patients with moderate or severe pain. In the studies by Cleeland et al. [4], Dorrepaal et al. [6], Brescia et al. [1], Larue et al. [18], and Zech et al. [31] on patients with other cancers, 45–98% of patients reported having pain.

The quality of the analgesic treatment yielded many reassuring aspects. A substantial proportion of patients was treated according to the WHO treatment steps: Many patients received opioids (43% of all visits and 58% of visits of patients with more than mild pain). Some authors described a higher percentage: 45–80% [1, 6, 9, 18, 27, 31]. In a high number of the visits in which opioids were prescribed, the opioids were combined with NSAID or paracetamol (64%). Only Zech et al. [31] reported a higher percentage of patients receiving the latter combination (73%). Many patients (51% of all visits, 71% of visits of patients indicating more than mild pain) received their analgesics as a fixed medication (by the clock). In patients with no or mild pain, administration of analgesics on demand may be adequate. Our proportion of visits with fixed medication is greater than in other reports: Vuorinen et al. [28] reported 39–63% of patients with regularly prescribed analgesics, Bruera et al. [2] 31–42%, Brescia et al. [1] 36%. Most patients received their basic medication as a peroral regime. In the more recent studies, we observed an increase in the use of transdermal systems. Only in exceptional cases was the basic medication administered subcutaneously. These recommendations were less frequently followed in patients with no or mild pain. The Cleeland index, a conservative indicator for the adequacy of the prescribed analgesics, was ≥0 in the majority of visits (≥0 in 63%, <0 in 23% of all visits). Cleeland et al. [4] described a higher number of cancer patients with a negative index (42%) and Larue et al. [18] an even higher number (51%). Surprisingly, we did not find a substantial improvement in the quality of the analgesic treatment over the decade when the SAKK trials were carried out.

Nevertheless, we identified deviations from the WHO guidelines. They are summarized in Table 4. From other studies, we know that a better treatment of cancer pain is possible: Ventafridda et al. [27] reached a successful treatment in 71% of patients by the adherence to the WHO ladder. Zech et al. [31] described a good pain relief in 76%, a satisfactory efficacy in 12%, and inadequate efficacy in only 12% of patients treated according to the WHO guidelines. Jadad and Browman [13] concluded that analgesia was adequate in 69–100% of the reviewed studies using the WHO guidelines.

Based on our study, we cannot be fully satisfied with the quality of pain treatment in Swiss cancer centers. This is a multifaceted problem. A major problem consists of the attitude towards cancer pain both of the patients and physicians. Patients tend to underreport the experienced pain [30], and many show reluctance to use opioids. Hence, the problem cannot solely be solved by improving the knowledge of the physicians; we need to intervene at various levels. Solutions on a national level include information campaigns to oppose the patients' "opiophobia". On an institutional level, patients should be encouraged to report their pain, e.g., by a corresponding hospital policy. To change the physicians' attitude is also a challenge. Education in Switzerland is good, but information alone may not be sufficient to change the physicians' practice [19]. National programs and institutional policies must be promoted to make physicians aware of the importance of analgesic treatment in cancer patients. Less experienced colleagues need support from superiors or a pain service. Institutions should promote the use of graphic tools to make pain visible. Training programs should also improve the physicians' communication skills [8, 10, 19].

Conclusions

In this selective sample of patients with advanced prostate cancer treated in Swiss cancer centers, we found a good quality of analgesic treatment. However, further improvement on a national and institutional level is required to change the patients' attitude towards cancer pain to encourage patients to report their pain and to improve the knowledge and communication skills of the physicians.

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