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INVITED ARTICLE

Does palliative chemotherapy provide a palliative effect on symptoms in late palliative stages? An interview study with oncologists*

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ABSTRACT

Background: The possible chemotherapy effects on symptoms in late stages of palliative chemotherapy are seldom registered in clinical practice or investigated as primary outcomes. The aim was therefore to study physicians' opinions and experiences about chemotherapy effects on symptoms.

Material and methods: Thirty-five physicians (mainly oncologists) with variation as regards age, gender and experience were included in a qualitative study with semi-structured interviews. A qualitative content analysis was used for the 30–60 min long interviews.

Results: According to all the informants, symptoms were possible to control in successful cases but the chances reduce rapidly with the number of chemotherapy lines. Symptoms possible to control included various types of pain (bone pain, neuropathic cranial as well as meningeal nerve pain, colic pain, "liver" pain, headache and pain from cutaneous metastases); nausea and vomiting caused by obstruction; dyspnoea due to pleural effusions or bronchial obstructions. Also fatigue and B-symptoms were possible targets, as were diagnosis-specific symptom clusters (e.g., liver metastasis causing pain, nausea, tumour fever and night sweats; or head–neck cancers resulting in nerve pain, ulcerations, odour, dysphagia and impaired breathing). Some of the oncologists discussed whether the effects were related to chemotherapy treatment only or partly to premedication with steroids. Despite the claimed effects, the physicians did not keep record on symptoms, they did not evaluate them with validated instruments.

Conclusions: Palliative chemotherapy has a substantial potential to reduce agonizing symptoms especially in first line treatments, but the effect is limited in late stages. The actual awareness of and knowledge about situations where the treatment has a reasonable potential, should be improved and symptoms should be monitored during treatment.

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Introduction

Chemotherapy and targeted therapies are nowadays a mainstay in the treatment of disseminated cancers, as they may provide both life prolongation and symptom control, resulting in better health-related quality of life (HRQoL). As regards life prolongation, this is mainly true for first-, and second-line treatments, whereas further treatments may or may not give clear-cut benefits [1–6] and modern palliative treatment is rather expensive [7]. There is even a common perception that palliative chemotherapy treatments are used too generously to cancer patients at the end-of-life, with no obvious indications [8–11]. The patients are, therefore, at risk of spending too much time receiving treatments in the terminal phase with no or minimal survival benefits, in parallel with disturbing side effects that may reduce quality of life (QoL).

We know a lot about the effects of first-line treatments, as regards the effects of chemotherapy on symptoms such as pain, nausea, dyspnoea or bleeding. However, the benefit of third or more lines is ambiguous. As a rule, treatment guidelines only cover first- or second-line treatments, still palliative chemotherapy is prescribed even in EOL (end of life) situations. Moreover, when included in studies, symptoms are often analysed as secondary variables or as parts of HRQoL instruments, with limited details about symptoms.

However, there are some data on symptoms, mainly from first- or second-line treatments e.g., studies showing a potential pain reduction in hormone-refractory prostate cancer [12], and in a Cochrane review of 107 randomised studies it was concluded that pain relief was possible in 35–76% of the patients [13]. Similar pain-relieving effects are also seen in advanced pancreatic cancer [14], breast cancer [15], esophagogastric cancer [16] and various solid cancers [4,17]. As regards lung cancer, pain, dyspnoea and emotional functioning is reported to improve by palliative chemotherapy [18]. In addition, other studies support the opinion of a symptom-relieving effect in various types of cancers, even if symptoms are seldom the focus of the study [17].

Thus, there is some evidence in favour of palliative chemotherapy for the alleviation of cancer symptoms, but data are mainly collected from early palliative stages, not from EOL situations. There are also two problems with most studies: In many studies corticosteroids were provided as anti-emetics in conjunction with the chemotherapy treatments.

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It is well known that corticosteroids exert a substantial effect on cancer symptoms e.g., on bone pain, nausea and dyspnoea [19,20]. This is not a problem in first-line treatments, as complete or partial responses go in parallel with symptom reduction. However, in EOL situations when multiple chemotherapy lines already have been prescribed, an ineffective treatment may be masked by symptom improvement, produced by steroids. Furthermore, although effects have been registered for symptoms produced by metastatic cancers, the effects may be variable, depending on the type of cancer and the extent of the disease.

Aim

As systematic data are scarce, the aim of our semi-structured interview study was to explore the opinions and experiences of oncologists with focus on chemotherapy effects on cancer symptoms, in late stages of a disseminated disease, with special focus on third-line or more treatments.

Material and methods

Subjects

In total, 35 physicians working clinically with malignant diseases were included. We aimed at a maximum variation sampling [21], with reference to specialty (30 oncologists, three gynaecological oncologists and two haematologists); work place (four university hospitals, two central hospitals); experience (30 specialists with one to over 30 years of experience as a specialist, and five residents); gender (20 male and 15 female physicians).

The interviews

The semi-structured interviews were 30–60 min long, tape-recorded and transcribed verbatim. We used an interview guide that gave a general structure to the interview but the interviewer was free to use follow-up questions whenever needed for validation and further exploration of the answers. The main focus of the interviews was on the doctor's own experience, own impression and general knowledge about chemotherapy effects on symptoms in late stages on cancer. "Late stages of cancer" was presented by the interviewer as third *or more* lines, depending on cancer type, as a third line treatment is much less effective e.g., in a metastatic pancreatic cancer, than in a breast cancer.

The analysis

The discussions were recorded, transcribed in a slightly modified verbatim mode and analysed with qualitative content analysis with a manifest focus and no predefined codes [22]. The analysis, described as conventional content by Hseih and Shannon, was performed using the following steps:

1. The interviews were read through several times just to get familiar with the content.
2. Secondly, they were re-read systematically to identify meaning-units i.e., words or text segments, patterns of meaning and issues of potential interest with reference to the research question (in this analysis, focus was on symptoms and symptom clusters). The segments were also marked with a preliminary code.
3. In a third step those segments marked with similar codes were brought together and formed meaningful clusters (i.e., preliminary categories). As far as possible the actual words expressed by the informants were used.
4. Fourthly, the statements in each preliminary category were scrutinized and compared to find the central component and fused into categories.
5. Next, the final categories were compared to avoid obvious overlapping and in a last step the categories were compared and analysed in order to reveal possible relationships or hierarchies between them.

Ethics

The study was approved by the regional ethics committee.

Results

All informants stated symptom control as a main goal for palliative chemotherapy also in late stages, besides the limited chance for life prolongation. Still, relatively few of them had a well-reasoned view about which symptoms would be possible to alleviate for patients with a certain type of cancer or a specific pattern of dissemination, especially in EOL situations. At direct questions, most of the respondents mentioned relief of pain and improvement of the patients' general performance status (PS) as possible to obtain in cases where the metastases were responsive to palliative chemotherapy.

When posing more direct questions, also tumour-related symptoms such as fever, night sweat and weight loss (B-symptoms) were mentioned, as well as specified organ symptoms (due to mechanic pressure), effusions (pleura or ascites), nausea and dyspnoea (Table 1).

There was a consensus that improved symptom control went in parallel with objective tumour response in most cases and that the effects were most prominent with first- and second-line treatments, whereas the situation after three or more lines was different. However, the symptoms were difficult to evaluate. As one physician put it: 'How can you

Table 1. Categories and subcategories of symptoms and symptom clusters, possible to control under optimal conditions.

Performance status and quality of life
Fatigue
Pain relief
Nausea and vomiting
Dyspnoea
Skin problems
Organ-related symptom clusters
Gastro-intestinal symptoms
Head-and-neck symptoms

tell in the everyday clinical situation, as you don't have a control group? Is this fatigue due to cancer progression or a side-effect to the given treatment?'

In general, experienced oncologists had more detailed descriptions than younger colleagues and were more experienced in distinguishing between cancer symptoms and side-effects.

> I had this patient on Docetaxel. She responded but was so tired, no appetite and so on. I chose to stop the treatment and change to capecitabin and her general condition was really improved. She has appetite again and is more active. Evaluations show stable disease, so this was a better palliation, even though Docetaxel showed a greater objective response. (S 21, breast cancer oncologist)

In the interview this oncologist (S 21) deepened her view of palliative goals: As regards first-line treatments, her goal was obviously objective responses verified by x-ray examinations. However, in EOL situations, the subjective well-being and the reduction of symptoms and side-effects were even more important goals than objective findings.

No one made systematic follow-up of symptoms and especially in late stages (third-line or more treatments) some of the more experienced oncologists questioned whether possible effects on symptoms really were related to chemotherapy or to premedication with steroids.

Performance status and quality of life

Many of the respondents mentioned PS, QoL, general condition and fatigue interchangeably, without defining the concepts more precisely. There was a common understanding that patients who were responsive to palliative chemotherapy had a good chance to improve their PS, fatigue and QoL in general. In malignancies, well-known for producing tumour-related fever or night sweats, these symptoms were expected to respond, as chemotherapy had a good chance to down-regulate the cytokine production. In hematologic malignancies, this effect was sometimes prominent, sometimes with a rapid onset within days after a first chemotherapy treatment. As regards third-line or more treatments, most of the experienced oncologists stated that the chance to improve PS or decrease tumour symptoms was rather limited, still 'palliation' was the main goal of the treatment.

> If the treatment influences performance status and fever, well then I think it is because the chemotherapy down-regulates the cytokines. So –yes – you can get a pronounced effect on symptoms. (S 11, lung cancer oncologist)

> In general, it's either- or: Either you get a good effect on the disease and in those cases the patients will feel fine. Or, then you don't, and you see no effects. (S 17, haematologist)

Some of the respondents did not mention PS but listed spontaneously a number of symptoms that were responsive in certain cases.

> Well, of course you see an effect on pain, but also regression of ascites production, improved breathing, better appetite, improved well-being, a more alert and active patient … Yes, I think I have seen that in several cases. (S18, experienced oncologist)

Fatigue

Fatigue was often mentioned as an independent symptom, although it obviously was a part of the general condition. However, several informants stated that there was a realistic chance to relieve cancer-induced fatigue in certain palliative situations, whereas it was a different question in the adjuvant setting where progressive fatigue was considered to be a side-effect of the given chemotherapy. Some of the oncologists described the effect on fatigue to be diagnosis-dependent. As one respondent put it: 'I can see an effect on my sarcoma patients, but seldom on my G-I patients' (S15).

In general, younger oncologists were preoccupied with fatigue as a side-effect and were less likely to identify improvements in the general condition and reduction in fatigue that manifested itself after a few cycles of treatment. As a rule, all respondents stated that fatigue in late stages was seldom improved.

> Of course, if you have a marked effect in a cancer patient with severe symptoms, fatigue may very well respond. But you can have the opposite situation: a patient with few symptoms where chemotherapy is the main reason for fatigue. … // … In general, your chances are better if you have [cancer] fatigue in an early stage of your disseminated disease. (S 9, experienced breast cancer oncologist).

Pain relief

Almost all of the informants mentioned pain as the main symptom that was possible to relieve with successful palliative chemotherapy, even if the effect was described as partially depending on the underlying diagnosis. Bone pain in breast and prostate cancer were often mentioned as possible examples. Most of the informants mentioned pain in general terms, whereas a few of them obviously had analysed pain in their clinical work and, therefore, gave more detailed descriptions. As an example, a lymphoma specialist described different pain situations that were possible to manage with palliative chemotherapy: headache or neuropathic pain syndromes due to leptomeningeal spread; neuropathic pain due to pressure from enlarged retroperitoneal lymph glands; bone pain in newly diagnosed patients with myelomas. In head–neck cancer, effects on the typical neuropathic facial pain (pressure and inflammation of cranial nerves) were described in successful cases, even if most of these patients were difficult to manage.

Several of the oncologists specialized in gastro-intestinal malignancies described pain due to liver metastases as a typical pain that would respond, whereas some of them also mentioned colic pain and other pains related to a partial bowel obstruction. Pancreatic pain was also outlined as an entity, possible to relieve in responders. An oncologist with long experience of melanoma patients described a possible effect on the general pain from the whole body, especially the typical muscle pain sometimes seen in patients with massive spread of their disease.

> You know, there are these melanoma patients where the metastases just 'explode' in their whole body. They have an extreme spread of metastases and have some kind of diffuse,

> migrating pain. They have muscle ache, they have pain all over. Sometimes you can see a dramatic effect if they are responders, a dramatic effect! They can describe how the pain just vanishes like this (the oncologist makes a dramatic gesture in the air). (S 25, specialized in melanomas)

> You mean metastatic pain? Docetaxel may be of great value in prostate cancer and chemotherapy provides also pain relief in breast cancer. (S 22, experienced oncologist).

Even if pain was the most obvious symptom possible to control, only a few of the respondents made formal pain measurements and no one made a systematic follow-up.

Nausea and vomiting

Cancer-induced nausea was often perceived to be secondary to liver metastases, or to obstruction caused by gastro-intestinal cancer. Gastric cancer was mentioned as a concrete example. When nausea was related to pressure and/or inflammation, recovery was considered obtainable.

The potential nausea-relieving effect was more often mentioned by oncologists with a broad clinical experience. Even if nausea due to liver metastases was seen as the typical condition where a symptom control was possible, this was also debated as nausea was typical for wide-spread liver metastases and in such cases the risks associated with chemotherapy were increased. However, in most cases chemotherapy was expected to induce, not to relieve nausea.

> I prescribed chemotherapy to this nauseated patient with gastric cancer. He told me: 'I thought the treatment would cause nausea, but now it's the opposite situation! Finally, I can eat and feel well!' The tumour had shrinked rapidly already after the first or second cycle. (S 10)

Dyspnoea

Relatively few of the oncologists described dyspnoea as a part of the general condition, but made associations to specific situations: patients with pleural effusions or localized bronchial obstructions, or lung cancer patients with underlying COPD (chronic obstructive pulmonary disease). A few doctors associated dyspnoea with excessive ascites production.

> In many patients, you can obtain a regression of pleural effusions without pleural drainage. So, I tend to cool down and wait [for the response]. (S 11, specialized in lung cancer)

> [Lung cancer] patients with dyspnoea may respond. But as a rule, these patients already have disturbing dyspnoea from their COPD. The cancer adds to the dyspnoea, but not so much. (S 11, specialized in lung cancer)

Skin problems

Also subcutaneous metastases with or without ulcerations were mentioned as indications for symptom relief by the aid of chemotherapy. Such problems were frequently seen in patients with head-and-neck cancers, but also in malignant melanoma and in breast cancer patients. In rare breast cancer patients, the local subcutaneous metastases spread rapidly and formed an armour of confluent metastases, so-called 'en cuirass breast cancer' with caused discomfort, pain and a heavy pressure.

> I had this patient with cutaneous metastases, like an armour. She had tried everything without any effect. Then I prescribed Capecitabine (Xeloda®) and – this armour of cancer shrinked and this pressure was relieved and she could take deep breaths again. The effect lasted for three months. (S 21, breast cancer oncologist)

Organ-related symptom clusters

Some of the informants did not specify symptoms, but gave descriptions of symptom clusters related to specific organs.

Gastro-intestinal symptoms

A majority of the informants, irrespective of primary tumour, mentioned liver metastases as a source of several symptoms, including nausea, tumour fever and night sweats. Oncologists mainly working with gastro-intestinal cancers also described symptoms related to obstructions, to partial obstructions or to pressure e.g., appetite loss, colic pain, nausea, irregular or frequent bowel movements, problems sitting (due to rectal pain) or discomfort related to hydronephrosis. Some also included rectal bleeding and constant anaemia as problems. If the metastases were responsive to palliative chemotherapy, these symptoms were possible to control.

> Sometimes we see tumour reduction. Well, [in these cases] we can achieve effects on pain, sweats, general fatigue and tiredness, everything gets better. (S 24)

> Well, then this lady came back after her first course of palliative chemotherapy and said: 'Now I have appetite like a horse!' And she had chemotherapy with no steroids! I could also register a clear regression of her subcutaneous metastases. (S 32, about a patient with wide-spread intra-abdominal and cutaneous metastases)

Head-and-neck symptoms

Oncologists mainly working with head-and-neck cancers generally described a symptom cluster of pain due to pressure of cranial nerves, ulcerations, odour, dysphagia and impaired breathing. In some cases, they drew a picture of a horrible suffering that sometimes was possible to influence at least temporarily with the aid of palliative chemotherapy.

> Well, you can see effects in about 50% of the cases. …//… Mainly on pain, but also ulcerations, swallowing and so on. …//… but sometimes these patients are too fragile and not candidates for palliative chemotherapy.(S 8)

> The ulcerations and their swollen neck…//… I mean, even their tongue can be swollen and big. …//. I had this patient with this grotesque tongue that was protruding a few days before each cycle. Then he got his treatment and after a few days he could close his mouth again, at least temporarily. (S 32)

Discussion

There was a consensus with no exceptions that palliative chemotherapy aims at symptom control, besides hopes for prolongation of life. When discussing the relationship between the tumour-specific effects and symptoms, most of the respondents spontaneously stated that tumour response and symptom control tend to go in parallel: When an objective response is possible, the patient will also feel better as regards PS, QoL and well-being in general. Chemotherapy studies support this view, at least in first-line treatments, as objective responses often are accompanied by improvements in HRQoL [5,15].

However, when discussing *third or more lines of* treatments, the picture was ambiguous: even if there was a chance for improvements, most of the physicians expected increased fatigue, more problems with nausea and reduced PS because of burdensome treatments. Still, most of the respondents described at least a few successful cases with an obvious reduction of symptoms even in advanced obsolete cases. Such experiences were an incentive for further treatment of similar patients. However, none of the respondents kept record on such single successful events, in a systematic way.

Pain, nausea, and dyspnoea

Although all the respondents mentioned pain as a symptom that regularly responds to chemotherapy, only a few of them made formal pain assessments and as a rule they did not even measure pain intensity with VAS, NRS or other instruments. Instead they settled for more vague, verbal descriptions from their patients e.g., 'pain is improved.'

When they were asked to describe more in detail which types of pain are most likely to respond, the picture was scattered. Every oncologist described bone pain in prostate or in breast cancer as responsive, whereas the more experienced physicians were able to broaden their description and the total panorama was impressive: In successful cases pain alleviation was possible in bone pain, in neuropathic cranial nerve pain, in neuropathic leptomeningeal pain, in liver pain, colic pain and even in migrating generalized pain in metastatic melanoma patients. Thus, palliative chemotherapy has a great potential for the alleviation of cancer pain as already known for certain diagnoses [13,15–18]. Still, the scientific data are scarce and difficult to identify, even when using search terms such as *palliative chemotherapy, symptoms, quality of life, best supportive care,* in different combinations. This was especially true for late stages of palliative chemotherapy, which was the focus of this interview study.

A general understanding was that successful chemotherapy affects not only single symptoms, but symptom clusters: e.g., oncologists working with head-and-neck cancers described effects not only on pain, but also on ulcerations, odour, dysphagia, impaired breathing and even on swollen, protruding tongues. This observation raises an interesting question: Are all symptoms of a cluster equally responsive? And if so – what is the common, underlying cause? If we knew more about the mechanisms that produces disturbing and even agonizing symptoms, we would be able to tailor treatments that provide a more specific palliative effect.

Undoubtedly, inflammation is a general source of several cancer symptoms such as pain, appetite loss, fatigue and nausea. Therefore, steroids are often used for disturbing cancer symptoms [19,20]. For this reason, steroids are confounders in the evaluation of true effects of chemotherapy, especially in combination with third or more lines of treatment, where the true chemotherapy effect may be limited.

Still, we have reasons to believe that chemotherapy drugs may have the potential to produce an *independent* symptom reduction: If the cancer is controlled, also the release of pro-inflammatory and related factors are down-regulated [23], resulting in pain and symptom relief.

As an example, endothelins that are expressed in high levels in prostate cancer, are known to sensitize and excite certain nociceptors (TRPV1-receptors) [24], which means that an active cancer growth exacerbates and maintains pain. At the same time, the same factors (in this example endothelins in interaction with prostaglandins) also stimulate angiogenesis and tumour growth [24]. For this reason, they are potential targets *both* for tumour control *and* for the alleviation of symptoms.

Moreover, certain chemotherapy substances have also effects that are not related to cancer cell kill, but to the inhibition of host cells. Methotrexate is a well-known example: it inhibits macrophage activation and the release of interleukin-1 [25], therefore, it is used in low doses for rheumatic pain. Obviously, inflammatory metastatic pain has similarities with rheumatic pain which may explain why chemotherapy exert an effect on pain even in cancers with minimal or no objective tumour response, as the effect on host cells such as macrophages and white blood cells might be considerable, even in cases where the actual tumour cells are resistant.

Whereas progressive cancers with poor prognosis are associated with pain, also the opposite is true: Symptoms such as pain may *indicate* a poor prognosis. In a study by Bernhard et al. [26] in advanced pancreatic cancer, pain and tiredness were established as independent prognostic factors and this was also corroborated by Lord et al. [27] in elderly patients with gastroesophageal cancer: poor prognosis was predicted by presence of cancer symptoms and by poor PS.

According to the informants, especially the more experienced oncologists, symptoms and the potential symptom reduction are not merely related to the number of lines, but also to cancer type and to the setting. Patients with first-line treatment are more likely to benefit than those receiving third line or more treatment; patients with tumours normally sensitive to chemotherapy have better chances for positive effects but also patients with chemo-resistant tumours might benefit, at least regarding pain. And finally: tumour-free patients in an adjuvant setting are expected to experience fatigue as a result of the treatment, whereas selected patients with tumour-induced fatigue might become less tired and more active in successful cases. Some of these data are also corroborated by studies, but the positive effects are mainly limited to palliative first-line treatments [5,15].

Weaknesses and strengths with the study

In interview studies informants tend to remember exceptional cases which may not be representable for the total population. Therefore, they may exaggerate chemotherapy effects based on a recall-bias. However, most of the informants pointed out that substantial effects in far advanced cancer are rare.

A strength is that the interviews give valuable information about the *potential* of chemotherapy and the *type* of symptoms that may be possible to treat under optimal conditions. This is an important contribution, as systematic studies with cancer symptom relief as a primary outcome are lacking in advanced stages and in EOL situations. Still, palliative chemotherapy is used even during the last month of life [11,28]. When an individual symptom such as pain is mentioned in studies, it is normally only registered as a part of QoL questionnaires, which gives limited information about the type of pain (nociceptive or neuropathic), the localization and so on. Moreover, even if there are studies comparing chemotherapy treatment with 'best supportive care,' we do not have enough data today. In a review of 43 studies, it was concluded that 'best supportive care' is not a well-defined concept and that several studies have chosen 'standard care' instead of 'best supportive care' in the control arm [29].

Conclusions

In conclusion, our study shows that there is a range of symptoms that may be controlled with the aid of palliative chemotherapy. Some of these effects e.g., the effect on neuropathic pain, are easy to overlook. There is, however, a common understanding that the chances for a substantial effect diminish rapidly with tumour progression and the number of chemotherapy lines. This should be taken into account when considering further palliative chemotherapy 'for palliative reasons,' especially in cases where life prolongation no longer is a viable option.

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References

[1] Van Cutsem E, Peeters M, Siena S, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol. 2007;25:1658–1664.

[2] von Plessen C, Bergman B, Andresen O, et al. Palliative chemotherapy beyond three courses conveys no survival or consistent quality-of-life benefits in advanced non-small-cell lung cancer. Br J Cancer. 2006;95:966–973.

[3] Thatcher N, Chang A, Parikh P, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). Lancet. 2005;366:1527–1537.

[4] Bellmunt J, Theodore C, Demkov T, et al. Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. JCO. 2009;27:4454–4461.

[5] Mayrbaurl B, Giesinger JM, Burgstaller S, et al. Quality of life across chemotherapy lines in patients with advanced colorectal cancer: a prospective single-center observational study. Support Care Cancer. 2016;24:667–674.

[6] Mayrbaurl B, Wintner LM, Giesinger JM, et al. Chemotherapy line-associated differences in quality of life in patients with advanced cancer. Support Care Cancer. 2012;20:2399–2405.

[7] Starling N, Tilden D, White J, et al. Cost-effectiveness analysis of cetuximab/irinotecan vs active/best supportive care for the treatment of metastatic colorectal cancer patients who have failed previous chemotherapy treatment. Br J Cancer. 2007;96:206–212.

[8] Emanuel EJ, Young-Xu Y, Levinsky NG, et al. Chemotherapy use among Medicare beneficiaries at the end of life. Ann Intern Med. 2003;138:639–643.

[9] Harrington SE, Smith TJ. The role of chemotherapy at the end of life: "when is enough, enough?". JAMA 2008;299:2667–2678.

[10] Murillo JR Jr, Koeller J. Chemotherapy given near the end of life by community oncologists for advanced non-small cell lung cancer. Oncologist. 2006;11:1095–1099.

[11] Randen M, Helde-Frankling M, Runesdotter S, et al. Treatment decisions and discontinuation of palliative chemotherapy near the end-of-life, in relation to socioeconomic variables. Acta Oncol. 2013;52:1062–1066.

[12] Huan SD, Natale RB, Stewart DJ, et al. A multicenter phase II trial of losoxantrone (DuP-941) in hormone-refractory metastatic prostate cancer. Clin Cancer Res. 2000;6:1333–1336.

[13] Shelley M, Harrison C, Coles B, et al. Chemotherapy for hormone-refractory prostate cancer. Cochrane Database Syst Rev. 2006;CD005247. doi: 10.1002/14651858.CD005247.pub2

[14] Kristensen A, Vagnildhaug OM, Gronberg BH, et al. Does chemotherapy improve health-related quality of life in advanced pancreatic cancer? A systematic review. Crit Rev Oncol Hematol. 2016;99:286–298.

[15] Geels P, Eisenhauer E, Bezjak A, et al. Palliative effect of chemotherapy: objective tumor response is associated with symptom improvement in patients with metastatic breast cancer. JCO. 2000;18:2395–2405.

[16] Al-Batran SE, Ajani JA. Impact of chemotherapy on quality of life in patients with metastatic esophagogastric cancer. Cancer 2010;116:2511–2518.

[17] Bang SM, Park SH, Kang HG, et al. Changes in quality of life during palliative chemotherapy for solid cancer. Support Care Cancer. 2005;13:515–521.

[18] Roszkowski K, Pluzanska A, Krzakowski M, et al. A multicenter, randomized, phase III study of docetaxel plus best supportive care versus best supportive care in chemotherapy-naive patients with metastatic or non-resectable localized non-small cell lung cancer (NSCLC). Lung Cancer. 2000;27:145–157.

[19] Lundstrom SH, Furst CJ. The use of corticosteroids in Swedish palliative care. Acta Oncol. 2006;45:430–437.

[20] Shih A, Jackson KC. 2nd,. Role of corticosteroids in palliative care. J Pain Palliat Care Pharmacother. 2007;21:69–76.

[21] Patton MQ, Qualitative evaluation and research methods. Newbury Park: Saga Publications; 1990.

[22] Hsieh HF, Shannon SE. Three approaches to qualitative content analysis. Qual Health Res. 2005;15:1277–1288.

[23] Fitzgibbon D, Loeser J, Cancer pain. Assessment, diagnosis and management. Philadelphia: Wolters Kluver/Lippincott Williams & Wilkins; 2010.

[24] Pomonis JD, Rogers SD, Peters CM, et al. Expression and localization of endothelin receptors: implications for the involvement of peripheral glia in nociception. J Neurosci. 2001;21:999–1006.

[25] Johnson WJ, DiMartino MJ, Meunier PC, et al. Methotrexate inhibits macrophage activation as well as vascular and cellular inflammatory events in rat adjuvant induced arthritis. J Rheumatol. 1988;15:745–749.

[26] Bernhard J, Dietrich D, Glimelius B, et al. Estimating prognosis and palliation based on tumour marker CA 19-9 and quality of life indicators in patients with advanced pancreatic cancer receiving chemotherapy. Br J Cancer. 2010;103: 1318–1324.

[27] Lord SR, Hall PS, McShane P, et al. Factors predicting outcome for advanced gastroesophageal cancer in elderly patients receiving palliative chemotherapy. Clin Oncol (R Coll Radiol). 2010;22: 107–113.

[28] Nappa U, Lindqvist O, Rasmussen BH, et al. Palliative chemotherapy during the last month of life. Ann Oncol. 2011;22:2375–2380.

[29] Cherny NI, Abernethy AP, Strasser F, et al. Improving the methodologic and ethical validity of best supportive care studies in oncology: lessons from a systematic review. JCO. 2009;27:5476–5486.