Aims and reasons: ethical questions about palliative systemic anticancer therapy

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CHAPTER 1

GENERAL INTRODUCTION

Over the past decades the number of treatment options for patients with metastatic cancer has increased considerably. These are mainly palliative systemic anticancer therapies, which include chemotherapy, targeted therapy, hormonal therapy, and immunotherapy. The term ‘palliative’ indicates that there is no expectation of curing the disease. Decisions on the optimal time to start therapy and issues such as type of therapy, its intensity, duration, and possible changes to other treatment modalities are often difficult to make for both physician and patient.

Palliative systemic anticancer therapy is prescribed to prolong life and/or to improve quality of life. It is frequently prescribed, even close to the end of life. Treatment effects are dependent on the type and stage of the disease, the physical condition of the patient, and co-morbidity. Possible advantages for the patient need to be weighed up against the burdens of disease and toxicity. As metastatic disease progresses, treatment may become less effective, but may nonetheless be burdensome to the patient. Especially the value of a limited prolonging of life needs to be balanced with possible deterioration of the quality of life due to side effects and the complexity of treatment regimes. These complex considerations make the decision to start, forego, continue, discontinue or modify palliative systemic therapy an often ethically difficult one for both patient and physician to make. The problem addressed in this study is that it is often unclear what good use of palliative systemic therapy actually is.

The purpose of this project was twofold: firstly, to increase insight into the ethical problems associated with palliative systemic therapy (PST) in metastatic breast and colorectal cancer, both in the context of individual patient care and in guideline setting, and secondly, to develop a normative framework intended to support decision making in both these contexts. Whereas in individual treatment, financial considerations will usually play no significant role, these are likely to pose particularly difficult problems in the guideline setting.
The overall purpose of this thesis led to the following original questions:
1. What is the basis of value judgements of physicians and patients (and their next of kin), in individual patient care in metastatic breast or colorectal cancer, when deciding whether to start or not to start palliative chemotherapy, or to continue, discontinue, or modify treatment?
2. What role do normative considerations play when setting guidelines for chemotherapy in these patients?
3. What is a theoretically justifiable and practically useful normative framework that may support decision making in this area?

These original research questions were adapted during the process of this study as is one of the essential characteristics of qualitative research. The final research questions will be presented below.

1.1 What is ‘good use’ of palliative systemic therapy?

In the literature on palliative systemic therapy, two approaches to the question of good use of palliative systemic therapy are to be found. The first approach, which has developed within studies on patient-physician communication in metastatic cancer, is that good use of palliative systemic therapy is guaranteed when patients are well informed before treatment is started. It is hence a procedural approach. When patients are well informed and have made a balanced decision together with their doctors, the use of PST will be good.

Many studies have demonstrated that there is a wide variation in the quality of information provided to patients with advanced cancer. For instance, it is known that physicians give little information on prognosis and on the added value of treatment compared with supportive care. Physicians tend to inform patients about active treatment, whereas supportive care and watchful waiting are not often discussed. Another issue in the communication between physicians and patients is that physicians try to give hope to their patients. This in itself may not be wrong. The trouble is, however, that realistic information about imminent death is often not, or only partially given by the doctor and only partially received by the patient, so that unrealistic hopes for recovery may be nursed (this is sometimes called ‘collusion’).

These studies in patient-physician communication on palliative systemic therapy suggest that giving complete and understandable information to the patient is paramount. Only on the basis of solid information is the patient able to decide which form of treatment that he/she
wants. Giving good information is hence often seen as a sufficient condition for guaranteeing good use.

The second approach to the question of good use of palliative systemic therapy comes from an ethical-theoretical discussion in which *minimal principles* that participants should respect are formulated. Randall and Downie, one an ethicist, the other a palliative care physician, developed a normative framework especially for ‘possibly life-prolonging treatments’ in the palliative phase. This is the only publication found in the medical ethical literature that explicitly examines situations in which potentially life prolonging treatment such as palliative systemic therapy should be avoided. Their question is not: ‘when can systemic palliative treatment be prescribed in a good way?’, but ‘when shouldn’t it be given?’ Hence, Randall and Downie present four situations in which it is not justifiable to offer life-prolonging and life-sustaining treatments:

1. *‘When the carers believe the treatments are physiologically futile’.* The authors refer to futility as treatments which are ‘extremely unlikely to be successful’ (the example they give is that of a cardiopulmonary resuscitation in the palliative care setting).

2. The second reason for not prescribing life-prolonging treatments is ‘*when the professionals consider that, following a benefits to burdens/risks calculus, they are unwilling to give the treatment.*’ The authors hence argue against the idea that the only person who is able to draw the conclusions from this calculus is the patient. The role of the physician would then be to explain benefits and burdens and leave the decision to the patient. However, the authors believe that even explaining is not under discussion because ‘*there seems little point in raising the patient’s hope by mentioning a treatment, only to dash them again by explaining that the burdens and risks are so overwhelmingly greater than the benefits that the carer is not willing to provide the treatment*.’ So if the physician does not want to prescribe the treatment due to a negative burdens/risk calculus, he/she should not even suggest that treatment to the patient.

3. The third reason for not prescribing life-prolonging treatments is ‘*when in their professional opinion the treatment will not further the patient’s medical good because worse ways of dying (which the patient declines to discuss) are likely to ensue*.’ Randall and Downie give examples of ‘worse ways of dying’. Patients may die from head and neck tumours in different ways: asphyxiation, total dysphagia, catastrophic haemorrhage or pneumonia. If a patient develops dysphagia, and tube-feeding by gastrostomy is undertaken, then the patient is likely to live long
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enough to develop either tracheal obstruction or haemorrhage. The question then is what is worse: to die from pneumonia or total dysphagia or from asphyxiation or haemorrhage? According to the authors, physicians may refrain from offering treatment when they think it takes away the chance of dying in an appropriate, meaning for example the least painful, way. The exception would be if the patients are competent and already experiencing the factors which could severely compromise their quality of dying, and they would still want their life to be prolonged. Then, the authors say, the offer of a life-prolonging treatment should not be withheld.

4. According to Randall and Downie it is also morally justifiable not to offer life-prolonging and life-sustaining treatments ‘when the combination of resource constraints and justice requires that the treatments are given to patients who are more likely to benefit from them.’ This means that when resources are scarce, they should be used to benefit the patients who may have most to gain. Although I will examine this perspective of justice by interviewing physicians about considering costs of palliative systemic treatments, I found that if such considerations do play a part, then it is outside the consulting room (Chap. 4). Therefore in this thesis, I will focus on ‘good use’ in individual patients and leave this fourth argument about justice aside.

Both the procedural and the minimal principle approach are ethical theories, but they are not substantial theories. The question what is good use is not answered. The first approach presupposes, to state it simply, that good information will lead to good treatment. The second approach tells us what we should not do, but does not describe what is good. When the physician respects minimal principles, everything else is allowed. So if we want to develop a more substantial ethical theory, addressing the question what is good use of PST, we should know much more about the way in which PSTs are being used and why. To this end, I decided to take a closer look at the aims for prescribing and undergoing PST that the participants put forward in their practices and deliberations.

1.2 What are the aims?

The lack of explicit reflection in the literature on what good use of palliative systemic therapy could mean, was also reflected in my study of oncology practices. During interviews with medical oncologists, they told me they had difficulties in formulating what should be the main aim(s) of palliative systemic therapy. The fact that the use of the prefix
‘palliative’ had different connotation to them added to this difficulty. To some, palliative chemotherapy is almost a contradiction in terms because palliative treatments strictly should refer to interventions that are meant to improve quality of life, so not generate toxicity. For others, life prolongation cannot be easily separated from quality of life, for instance because a patient sees life prolongation as quality improvement. Particularly when oncologists talked about specific individual patients, they were cautious and often unsure whether decisions made were actually good, particularly when patients opted for aggressive treatments with uncertain effects.

The absence or lack of clarity about good use of palliative systemic therapy in both the literature and in oncology practice, raises the question of what the aims of such therapies could be. By studying oncology practices, not only by interviews but also by doing observations, I hoped to learn what aims are used, even if not always clearly formulated. By reflecting on these findings I want to gain insight in what good use of palliative systemic anticancer therapy might mean.

On the basis of these considerations, the central questions of this study have been rephrased as:

1. What are the aims of palliative systemic anticancer therapy for patients with metastatic cancer and which role do these aims play in practice?

2. How can these aims be morally interpreted? And how do these interpretations contribute to good use of palliative systemic therapy?

Before I start looking at answers, I want to present some relevant background information on palliative systemic therapy in cancer. Then I will delve into the philosophical-ethical discussion about treatment aims.

1.3 Palliative systemic therapy

About 81,000 people were diagnosed with cancer in the Netherlands in 2005. In the same year, 39,600 people died from cancer. (www.IKCnet.nl)

The chances of survival differ widely depending on the type of cancer and the stage of the disease at diagnosis. Approximately 50% of all cancer patients are cured. Surgery is the most important curative treatment for most cancers. Surgery can be combined with other forms of treatment to improve chances for survival further. When systemic therapy is given preoperatively it is called neoadjuvant (adjuvant means supplementary) systemic therapy. And when systemic therapy is given postoperatively it is called adjuvant systemic therapy. Radiotherapy is one of the
forms of treatment that can be given either pre- or postoperatively to improve the chances of cure. In inoperable or metastatic disease most, but not all (e.g. carcinoma of the testis and the ovary and some tumors found in children), cancers are incurable. If the disease proves incurable, then the patient is said to be in the non-curative phase and systemic therapy is given the prefix ‘palliative’ (which in this context just seems to indicate that cure is not the intention anymore).

1.3.1 Palliative chemotherapy and targeted therapy

If there is no chance of cure, many systemic treatment options for patients with metastatic cancer may still be available. Although initially we had decided to concentrate on palliative chemotherapy, during this study (which started at the end of 2003) several new treatment strategies (that were already under study at the time of writing the research proposal) were introduced into routine practice, including several forms of targeted therapy. Therefore we also included these treatment modalities in this study.

Systemic therapy includes a number of treatment modalities such as hormonal therapy, immune therapy, chemotherapy, and targeted therapy. Hormonal therapy interferes with the functions of the endocrine system. The best known examples of hormonal therapy are anti-oestrogen therapy (such as tamoxifen), and anti-androgen therapy. Examples of immune therapy agents include interferon and interleukin-2. Cytotoxic agents (chemotherapy) kill cells by interfering with DNA and RNA during cell division. Chemotherapy may reduce tumour size (complete or partial remission), or stabilize tumour growth (stable disease). The big disadvantage of chemotherapy is that it also affects normal cells and therefore has many side effects. Examples of these are hair loss, nausea, vomiting, fatigue, and febrile neutropenia (decreased total number of white blood cells increasing the risk of serious infectious diseases).

It was hoped that targeted therapy, e.g. therapy with monoclonal antibodies and small molecules, including angiogenesis inhibitors, would give fewer side effects than chemotherapy. However in clinical practice this seemed not to be the case. Targeted therapy works by blocking crucial proteins with aberrant activity in cancer cells, or by blocking the growth of new capillaries around tumour tissue. Proteins, mostly involved in important signalling cascades, are also important for the regulation of normal cell metabolism, proliferation, and cell death. This explains why this still called ‘targeted’ therapy is toxic and may harm the patient. Examples of its side effects are cardiac failure, severe skin rash, stomatitis, diarrhoea, fatigue and gastrointestinal perforation.
1.3.2 Focus on colorectal and pancreatic cancer

A study investigating the proper use of palliative systemic therapy cannot hope to discuss all forms of PST in all forms of metastatic cancer. To be able to get in-depth understanding it is necessary to focus on a limited number of forms of cancer. Therefore, one should select the examples in such a way that the results of the study will still be relevant to a broad variety of cancers and treatments in the palliative phase. In the original study plan, colorectal and breast cancer were the focus of the study. However, because both these cancers are relatively therapy-sensitive in the metastatic phase, we felt that it might be more appropriate to compare colorectal cancer with a form of cancer that is less sensitive to therapy and is therefore a more severe form of metastasized carcinoma: pancreatic cancer.

Hence, metastatic colon cancer and metastatic pancreatic cancer are the case-studies in this thesis. Both are gastrointestinal cancers but have different palliative treatment options and clinical outcomes. Metastatic colorectal carcinoma is relatively chemotherapy and targeted-therapy sensitive; with several lines of systemic treatments in various phases of disease, life prolongation is considerable. Conversely, metastatic or locally advanced pancreatic cancer has a very poor prognosis with limited treatment options, restricted to first line treatment only. The process of decision-making on the optimal use of palliative systemic therapy in these two cancer types is probably very different.

Colorectal cancer

Colorectal cancer ranks second to lung cancer as a cause of death in the United States.\footnote{10} In the Netherlands 10,851 people were diagnosed with colorectal cancer in 2005, and 4,562 patients died in the same year due to this disease.\footnote{www.IKCnet.nl} Due to recent developments in treatment modalities, advanced colorectal cancer, a type of tumour that 15 years ago had only minimal treatment benefit, is now a tumour for which many treatment options are available. Life duration has improved considerably: the median survival for metastatic colon cancer has improved from about eight months to more than 20 months.\footnote{11,12} There are three active chemotherapeutic agents (5-fluorouracil(5-FU)/capecitabine, oxaliplatin, irinotecan) and three targeted agents (bevacizumab, cetuximab, and panitumumab) available for colorectal cancer which are administered in various lines of treatment, sequentially or as combination therapy.\footnote{11,12}

The disadvantage of combination therapy is that it generates toxicity.
whereas its advantage is not yet clear. A small subgroup of colorectal
cancer patients probably benefits from combination therapy but most
patients probably do not.\textsuperscript{13} Selection criteria for who benefits and who
does not benefit from combination or sequential therapy are not yet
available. The development of the oral 5-FU analogues, capecitabine and
UFT, has resulted in replacement of intravenous 5-FU as monotherapy
and in combination schedules. This may be an advantage for patients as
fewer hospital visits and IV infusions are involved. Quantitative data on
the use of these treatment options are not available. Most patients
(especially under the age of 75) undergo 2 to 3 lines of therapy.

\textbf{Pancreatic cancer}

Pancreatic cancer is the fourth cause of cancer-related death in the United
States.\textsuperscript{14} In 2005 in the Netherlands, 1,777 people
were diagnosed and 2,176 people died of pancreatic cancer.\textsuperscript{15} Unlike in colorectal cancer, the benefits of systemic therapy
in patients with pancreatic cancer are very limited. Gemcitabine is regis-
tered for the treatment of pancreatic cancer, mainly because the
improvement of symptoms during therapy.\textsuperscript{14,15} The median life prolon-
gation is very limited, about 4 weeks.\textsuperscript{14} Despite the availability of new
agents, hardly any progress in the treatment of metastatic disease has
been made over the last decade. The median survival is 8 to 12 months
for patients with locally advanced, unresectable cancer, and only 5 to 6
months for those with metastatic cancer at presentation. Data on the
use of systemic therapy in pancreatic cancer are not available. Considering
the limited treatment options in advanced disease, systemic therapy is
sometimesforgone. Nevertheless, at the same time a lot of patients are
treated with gemcitabine for metastatic and locally advanced disease.
Some centres prefer radiotherapy for locally advanced disease, a treat-
ment option with minimal life prolongation benefit, but which some-
times has proven to have a good effect on pain.\textsuperscript{16} Within clinical trials
numerous patients are being treated with gemcitabine in combination
with specific targeted therapies in order to ultimately improve progno-
sis for patients with pancreatic cancer.

\textbf{1.4 Aims of medicine}

In this section, I will discuss the potential aims of palliative systemic
therapy from the point of view of the ethical-philosophical literature.
Does this literature help in determining the aims of palliative systemic
therapy in oncology practice? In 1996, as a part of a project hosted by the bioethical research institute The Hastings Center, an international team of experts (among which were physicians and ethicists) formulated what they called ‘four goals of medicine’.\textsuperscript{17} They reached the articulation of these goals by discussion and deliberation (without empirical research into aims-in-practice). We will discuss these global aims one by one to see if they give an indication of what the treatment aims of palliative systemic therapy may be. They are the following and their order is arbitrary:

1. The prevention of disease and injury and the promotion and maintenance of health.
2. The relief of pain and suffering caused by maladies.
3. The care and cure of those with a malady and the care of those who cannot be cured.
4. The avoidance of a premature death and the pursuit of a peaceful death.

1. Prevention

Even though prevention may sometimes be an aim in the treatment of patients with metastatic cancer (for instance, when radiotherapy is used to prevent a spinal cord lesion due to bone metastases), PST is hardly ever used for prevention. Therefore, prevention is not relevant for my discussion of PST.

2. Relief of pain and suffering

In 1993 Porszolt and Tannock defined the critical endpoint of anticancer therapies when applied in incurable situations as ‘the relief of suffering rather than prolongation of existence’.\textsuperscript{18} At that time, in most tumours the gain in terms of prolongation of life was extremely limited. A number of years later, and partially prompted by new scientific developments, physicians began to call for prolongation of life to be given a more prominent position, even in incurable disease.

The Dutch Health Council report published in 2003 clearly stated that the most important aim should still be improvement in quality of life: \textit{Palliative chemotherapy is defined as intended to increase Quality of Life (QoL) and, if possible, also prolonging life with preservation of QoL.}\textsuperscript{19} However, many oncologists disagreed with the emphasis on QoL-improvement in this report; in their opinion, palliative chemotherapy should be primarily intended to prolong life. They argued that patients may attach great importance to a survival gain of sometimes only a few weeks or months.\textsuperscript{20} Secondly, they said that if improvement of QoL was the main
aim, the use of often burdensome palliative chemotherapy in asymptomatic patients would be unjustifiable.\textsuperscript{21}

As long ago as 1982, Cassel pointed out that achieving the aims of medicine (which he defined as ‘relief of suffering and cure of disease’), is not easy: ‘Physicians’ failure to understand the nature of suffering can result in medical intervention that not only fails to relieve suffering but becomes a source of suffering itself.’\textsuperscript{22}

Relief of pain and suffering certainly may be one of the aims of palliative systemic therapy. However, to what extent systemic therapy can be used to achieve this aim is controversial, especially as the treatment itself may become a source of suffering.

3. Care and cure

Cure is an unreachable goal for almost all patients with metastatic cancer. The prefix ‘palliative’ in PST in its most simple meaning indicates this namely that there is no expectation of curing the disease (anymore). At this point than really only care is left. But what is care? In a paper by the team of experts that further specifies the goals formulated in the Hastings Center Project, care is defined as follows: ‘Care is not simply the manifestation of concern, empathy, and a willingness to talk with patients. It is also a capacity to talk and listen in a way that is cognizant of those supportive social and welfare services needed to help people and their families cope with the wide range of non-medical problems that can and usually will accompany their illness. Of necessity, good caring demands technical excellence as a crucial ingredient.’\textsuperscript{23} This definition of care does not seem to be very helpful here. Although it is remarkable that care is formulated as one of the four goals of medicine at all. It turns philosophical concepts: care is usually seen as means to come to an end and not as an end in itself.

But even if we accept that ‘care’ is a goal in itself, the question here is if palliative systemic therapy can be interpreted as care. I relate this question to discussions about definitions of palliative care, which mainly differ on the perceived starting point of palliative care. Although, as I said, the simple meaning of a palliative treatment just seems to indicate that cure cannot be achieved, palliative care has different meanings. Palliative care is given in an effort to achieve physical, psychological, social and spiritual well-being for the patient. Two different ideas exist about when palliative care should be started. The first idea is that palliative care starts if other life-prolonging treatments have become futile.\textsuperscript{24} The second idea is that palliative care starts right at the beginning of a life-threatening disease and can co-exist with active treatments.\textsuperscript{25}
The first idea about the start of palliative care seems to exclude the use of anticancer therapies. However, it seems that according to this idea, only if palliative systemic therapy is given to improve quality of life might it be interpreted as palliative care. The second idea that states that palliative care can be combined with all forms of treatment obviously allows for systemic anticancer therapy as a part of palliative care. The twofold aim of cure and care which we discuss here does not seem to fit all instances of palliative systemic therapy: this treatment does not cure and it is hard to always interpret it as care, unless prolongation of life by no more than a few months counts as either cure or care. Let me conclude that care may be an aim of palliative systemic therapy but that this therapy certainly is not always used to achieve this aim.

4. Avoidance of death and peaceful death

Avoidance of a premature death and the pursuit of a peaceful death is again a twofold aim. For instance, nowadays the life of someone with metastatic colorectal cancer, can be prolonged substantially by the many treatment options available. Therefore, death after 8 months instead of 20 may be seen as premature. However, all these treatments will eventually affect the way of dying too: is the patient able to face death while he/she is still actively being treated? Will the patient die at home surrounded by family or die in the hospital due to the side effects of treatment? The avoidance of a premature death and the pursuit of a peaceful death may be contradictory aims, especially with regard to palliative systemic therapy. PST may be given with the aim of a modest prolongation of life, and for a better quality of life, but avoiding a painful death does not seem to have a place among these aims.

My overall conclusion about the ‘goals of medicine’ formulated by the international team of experts in the Hastings Center project, is that they do not fully describe the aims of palliative systemic therapy. Relief of pain and suffering may be the aims behind PST, and so may the care of those who cannot be cured, but what is absent from this list of goals is the complexity of determining the aims of palliative systemic therapy in various areas of oncological practice. The reason why the goals defined by the Hastings Center project do not seem to describe the aims of PST may be a methodological one. We will turn to that possibility in the next section.
1.5 Need for empirics

In order to capture the details of, and the interplay between, the aims of palliative systemic therapy in cancer, the practice of this form of treatment needs to be studied \textit{empirically}. In particular, qualitative research which strives for in-depth understanding of practices, enables us to find out how, in practice, physicians and patients not only talk about but also deal with and think about palliative systemic therapy, how they shape aims, and how tensions between aims are dealt with.

Three areas of practice are particularly relevant to this study: 1) research, where the development of new forms of therapy may introduce new aims; 2) guideline development, where - among other things - the goals of therapy are codified; and 3) clinical care, where treatment aims are given their final shape in the interaction between patients and doctors. In order to study each of these practices I have used a specific combination of methods. To study research practice I analysed aims that could be identified in published research papers. For reasons of feasibility and because the main focus of this project was on the clinical practice, I studied results of the research practice, and not the research practice itself.

To study guideline development I analysed guideline documents, both definitive and provisional, observed guideline working group meetings, and interviewed key members of working groups on guidelines.

To study clinical practice I did participant observation of outpatient consultations, and conducted three sequential interviews with patients and single interviews with individual treating physicians. Details about these methods are discussed further in the relevant chapters.

Studying the practices of research, guideline development and clinical care allows for an analysis of the aims that those involved operate with, even if they often cannot or do not formulate them themselves. The analysis shows what people in actual practice consider important and of value. These empirical findings then will to be followed by normative reflection: how can the aims identified be related and morally weighed?

1.6 Outline of this thesis

This thesis is structured as follows. \textit{Chapter 2} presents a review that answers the question about the aims of chemotherapy in RCTs in the palliative setting. Prolongation of life and improvement of quality of life are the main candidates. How are they weighed up against each other in research practice? \textit{Chapter 3} is an observational study that focuses on the question which value judgements and treatment aims are implicitly
incorporated in oncology guidelines. Chapter 4 presents an interview study in which physicians are asked about their role regarding costs: do costs limit treatment possibilities of potentially beneficial systemic treatments? Chapter 5 presents a case study about clinical care in which the process that leads to initiating, modifying, and stopping PST is analysed to see how the treatment gets shape and what the role of aims is. Chapter 6 analyses the ethical question if prescribing treatments that are probably ineffective (‘aimless’) but deeply wanted by patients, can be justified. Chapter 7, the general discussion, answers and discusses the central research questions; it also makes methodological reflections upon this empirical ethical study.
CHAPTER 1

Reference List


