Characteristics, Treatment and Prognostic Factors of Patients with Gynaecological Malignancies Treated in a Palliative Care Unit at a University Hospital

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Summary

Background: Limited clinical data have been published on patients suffering from advanced gynaecological malignancies treated in palliative care units, and little is known about prognostic factors. Methods: In a retrospective study, the data of 225 patients with breast, ovarian and cervical cancer treated in the palliative care unit of a university hospital between 1998 and 2009 were assembled. Clinical aspects and baseline symptoms, laboratory parameters, the clinical course, and outcome were evaluated. Results: 225 patients (497 cases; cancer diagnoses: breast 79%, ovarian 13%, and cervix 8%) were included in the analysis. The main symptoms were weakness/fatigue (71%), pain (65%), anorexia/nausea (62%), and dyspnea (46%). Pain control was achieved in 85% of all cases, satisfying control of other symptoms in 80%. The median overall survival (OS) was 59 days. 53% of the patients died at the palliative care unit. In the Cox proportional hazards model, 8 parameters indicated an unfavourable outcome: anorexia/nausea, disordered mental status, elevated lactate dehydrogenase, γ-glutamyltransferase, leukocyte count, hypoalbuminaemia, anaemia and hypercalcaemia. Based on these parameters 3 risk groups were defined: low risk (0–2 factors), intermediate risk (3–5 factors), and high risk (6–8 factors). Median survival for high-risk group was 13 days, for intermediate group 61 days, and for low-risk patients 554 days (p < 0.0001). Conclusion: Weakness/fatigue, pain and anorexia were the main symptoms leading to the hospitalisation of patients with gynaecological malignancies. Symptom and pain control was accomplished in 80% of cases. 8 parameters were identified as indicating a poor outcome, and patients showing at least 6 or more of these factors had a very limited prognosis. Although studied retrospectively, these results may be helpful for individual treatment decisions in patients with advanced gynaecological malignancies. Prospective data and the introduction of documentation systems could help to gain more powerful knowledge about the quality of palliative care.

Keywords
Gynaecological malignancies · Palliative medicine · Prognostic factors

Zusammenfassung


Schlüsselwörter
Gynäkologische Malignome · Palliativmedizin · Prognosefaktoren
Introduction

Gynaecological malignancies are the most common tumours of women in western industrialized nations. For example, in 2006, of the 197,600 women with newly diagnosed malignancies in Germany, about 37% suffered from tumours of breast, ovaries and cervix. Breast cancer is currently the most common newly diagnosed type of cancer with an incidence of 29% [1] in German women. For a long time international research and public promotion have focussed predominantly on curative and supportive therapeutic measures, such as prevention and treatment of nausea and vomiting in consequence of tumour therapy. Little is known, however, about the fate of patients in a palliative care situation. The discussion about euthanasia at the end of life and problems of adequate treatment of critically ill and dying patients underline the importance of an appropriate palliative care treatment near the end of life [2, 3]. It is, therefore, necessary to analyse medical care reality at palliative institutions such as palliative care units and hospices, and to determine relevant prognostic factors in terminally ill patients to optimize their treatment in the palliative care setting. Here, we report the findings of a retrospective study on patients with gynaecological cancer treated at a single-centre palliative care unit over an 11-year period. We were mainly interested in 4 questions: (i) Which complaints led to patient hospitalisation? (ii) Could an adequate symptom and pain control be reached? (iii) What was the fate of these patients (place of death; survival?) and (iv) Can specific prognostic factors be determined to establish a prognostic model?

Patients and Methods

We used the prospectively collected database of the palliative care unit, Mannheim University Hospital, Germany, and identified all patients with gynaecological tumours (breast cancer, ovarian cancer and cervical cancer) treated at the palliative care unit between June 1998 (set up of the palliative care unit) and December 2009. During this 11.5-year interval, 225 patients with gynaecological malignancies were documented. Many of these patients were treated in the palliative care unit several times. In total, 497 admissions (in the following referred to as ‘cases’) were counted. The following data were collected from the records: ‘personal data’ (age, weight, height, duration of hospitalisation, number of re-hospitalisations), ‘tumour data’ (tumour type, initial diagnosis, date of metastasis, location of metastasis), ‘symptoms and signs on admission’ (weakness/fatigue, pain, dyspnea, constipation, anorexia, nausea/vomiting, ascites, weight loss, pleural effusion, cough, infection, fever, dehydration, neurological disorders, vaginal or anal bleeding, diarrhoea, ileus, confusion/cognitive impairment, ascites, oedema, icterus and renal failure), ‘laboratory values’ (haemoglobin value, leukocyte count, thrombocyte count, lactate dehydrogenase (LDH), serum albumin level, electrolytes, γ-glutamyltransferase (GT), alanine amino transferase (ALAT), aspartate amino transferase (ASAT)), ‘treatment/interventions’ (medical treatment for pain according to World Health Organization (WHO) pain ladder and method of application, blood transfusion, parenteral nutrition, administration of chemotherapy, antibiotics or bisphosphonates, bladder catheter, radiation, pleural puncture and other therapeutic procedures, including treatment of heart failure (if indicated), pleurodesis with different techniques, intercostal drainage and chemotherapy, in cases with chemo-sensitive malignant pleural effusion, paracentesis), ‘outcome/fate’ (improvement of symptoms/pain, weight at discharge, parenteral nutrition at discharge, place and date of death). Survival was calculated according to method of Kaplan and Maier using the date of first admission to the palliative care unit as starting point. Univariate analyses (log rank tests and Gehan-Breslow-Wilcoxon tests) were conducted using Microsoft Excel (Microsoft Office, Version 2010) and Graph Pad Prism 5.0 (Graph Pad Software Inc., San Diego, USA). Multivariate analyses were performed by the Department of Biostatistics at the Deutsches Krebsforschungszentrum (DKFZ), Heidelberg. Regression analysis of survival data was performed based on the Cox proportional hazards model and using the conditional logit regression with the SAS PHREG procedure. Stepwise forward selection and backward elimination methods were used [4, 5]. 2-sided statistical significance was set at 0.05.

Results

A total of 225 patients (497 cases) with a median age of 65.5 years were evaluated. The range of hospital stays was 1–16. Both the youngest (30.3 years) and the oldest patient (91.8 years) suffered from breast cancer. 155 patients (68.9%) were older than 60 years on the day of first admission. Patient characteristics are summarized in table 1 (www.karger.com/?DOI=000355642). The most frequent diagnosis on admission was breast cancer (79.1%, n = 178). Less frequent diagnoses were ovarian (12.4%, n = 28) and cervical cancer (8.5%, n = 19). The few male patients with breast cancer were excluded.

Symptoms

Symptoms are recognised as indicators of poor survival in patients with advanced cancer [6, 7]. The distribution of symptoms and signs on admissions are shown in table 2 and table 3 (www.karger.com/?DOI=000355642). Table 2 considers all admissions and table 3 only the first admission at a palliative care unit. For most patients, several symptoms caused the need for inpatient treatment. The most frequent symptoms on admission were weakness/vertigo in 353 (71.0%) and pain in 321 (64.6%) cases; in 306 cases, patients complained of anorexia (61.6%); 248 cases (49.9%) had a pleural effusion; 227 (45.7%) suffered from dyspnoea and 205 (44.3%) from nausea/vomiting. Less frequent causes of admission were dehydration (n = 116; 23.3%) and confusion/cognitive impairment (n = 91; 18.3%). The leading symptom of patients with breast and ovarian cancer was weakness/vertigo, while patients with cervical cancer most often suffered from pain. It was remarkable that anorexia and nausea/vomiting were listed frequently as symptoms on admission in patients with ovarian cancer.

Blood Test Results

All blood samples were analyzed at the Institute for Clinical Chemistry of the University Hospital Mannheim. The
standard values of this institution were used as reference. The haemoglobin value was available for 483 (97.2%) cases, of which 368 (76.2%) had anaemia on the day of admission with a median haemoglobin level of 10.8 g/dl. In 174 (36.0%) cases, the haemoglobin concentration was below 10 g/dl. Anaemia (haemoglobin level under 12 g/dl) was more frequently noticed in patients with cervical cancer (96.4% vs. 76.2% in general). Leukocyte counts were available for 481 (97.2%) cases. Normal white blood cell (WBC) counts were recognised in 315 (65.5%) cases; 87 (18.1%) had leukocytosis, 16.4% (n = 79) had leukopenia. Thrombocyte counts were available for 478 (96.2%) cases. Elevated thrombocyte counts were recognized in 101 (21.1%) cases; 293 (61.3%) had normal platelet counts, 17.8% (n = 84) had thrombocytopenia. LDH activity was determined for 453 (91.2%) cases on the day of admission and was elevated in 274 (60.5%) cases (median LDH 284 U/l). Serum albumin was available for analysis in 449 (90.3%) cases. A low level of albumin was noted in 323 (71.9%) cases. The median blood albumin was 30.1 g/l. Notably, every patient with cervical cancer had hypoalbuminaemia. Albumin-corrected calcium levels were calculated for 445 (89.5%) patients. Hypercalcaemia was noted in 74 (16.6%) and hypocalcaemia in 51 (11.5%) cases. 37.0% of patients with cervical cancer had hypercalcaemia and none had hypocalcaemia. The median albumin-corrected serum calcium level considering all patients was 2.41 mmol/l. γGT activity was determined for 444 (89.3%) cases and was elevated in 303 (68.5%) cases (median 84 U/l).

Symptomatic Treatment during Hospital Stay

Table 4 (www.karger.com/?DOI=000355642) depicts the treatments administered to the patients during hospitalisation at the palliative care unit. A high percentage of patients continued to receive chemotherapy for symptom control. Intravenous therapy consisting of blood transfusion, parenteral nutrition and intravenous antibiotic therapy was analysed for each specific cancer group. Cervical cancer patients received antibiotic therapy more frequently (55.2%) than patients with breast cancer (39.5%) or ovarian cancer (48.3%), while parenteral nutrition was needed more frequently for ovarian cancer patients (48.3%) compared to breast cancer (29.8%) and cervical cancer (24.1%) patients.

Pain and Symptom Control at Discharge

Only 62 of the 497 cases did not need any pain therapy (14.3%). The other patients received therapy according to the WHO schedule; 65.5% required WHO 3 pain therapy. Most medication was necessary for patients with ovarian cancer, while cervical cancer patients required the least.

Pain was measured subjectively, according to a scale of 0–10, by the patient herself at the point of admission and at discharge. Overall, pain reduction, defined as no pain at all (0) or slight pain (1) if an improvement to admission was recognised, was achieved in 272 cases (84.7%). Ovarian cancer patients presented the best pain control (91.3%) at discharge, cervical cancer patients the worst (61.9%).

An indication for symptom control was given by written statements about the general condition in the patients’ records. In 80.3% of the cases where patients could be discharged, symptom improvement was recognised. Breast cancer patients achieved the best (81.2%), cervical cancer patients the worst (68.1%) symptom control.

Survival and Place of Death

Survival of patients was calculated from the first day of admission to the palliative care unit. Median survival was 59 days (Fig. 1). Most of the patients died at the palliative care unit (n = 115, 51.1%). 13.7% (n = 28) of the patients died within the first week of their stay, 26.7% (n = 60) during their first stay at the palliative care unit. 24.0% (n = 54) died at home, while 31 (13.8%) patients died at a hospice. 5 (2.2%) patients died in other medical institutions. 7 (3.1%) patients were still alive at the time of analysis, and 13 (5.8%) were lost to follow-up.

Analysis of Prognostic Factors

Clinical and blood parameters were evaluated by univariate analysis for possible influence on survival. The significance
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Survival Prediction Model According to Prognostic Factors

To predict survival time for individual patients at their first admission to palliative unit, the 8 identified prognostic factors were each assigned 1 point. For 175 (77.7%) patients, all 8 prognostic factors were known. On the basis of the presence or absence of the risk factors 3 risk groups were set up: (i) patients exhibiting 0–2 risk factors (low-risk group; n = 23), (ii) patients with 3–5 prognostic factors (intermediate-risk group; n = 113), and (iii) patients with 6–8 prognostic factors (high-risk group; n = 39). Survival analysis was performed using the Kaplan-Meier method. Patients in the low-risk group had a median survival of 554 days, in the intermediate-risk group 61 days, and in high-risk group only 13 days (p < 0.0001).

Discussion

Little is known about symptoms, treatment, medical care quality and prognostic factors in the palliative context. The majority of literature regarding palliative care does not differentiate between specific cancer groups, but considers palliative oncological patients in general. This is the first effort to describe the most frequent symptoms leading to hospitalisation (albeit symptoms were not assessed throughout according to a standardised assessment system, apart from pain), the quality of care and the outcome for gynaecological patients at an oncologically focussed palliative care unit, and to analyse specific prognostic factors that influence patients' survival.

We found weakness/vertigo (71.0% of all cases), pain (64.4%) and anorexia (61.6%) to be the most common symptoms of gynaecological patients at admission to the palliative care unit. Teunissen et al. [9] conducted a systematic literary research and found fatigue syndrome (74.0%), pain (71.0%), lack of energy (69.0%), weakness (60.0%) and anorexia (53.0%) to be the most frequent symptoms of palliative oncological patients unless they were terminal (last 2 weeks of life). This correlates with our findings. However, a more heterogeneous group was considered compared to our patients.

A higher percentage of patients with cervical cancer suffered from infections (58.6%) and renal failure (55.2%), and showed leucocytosis of over 11,000/µl (39.3%) more frequently than ovarian or breast cancer patients. These patients also needed more antibiotic therapy. This has not been described before in the general literature. Elevated leucocyte counts could hint at an infection, but may also be part of a paraneoplastic syndrome [10] perhaps due to the increased expression of granulocyte colony-stimulating factor (G-CSF), granulocyte/monocyte colony-stimulating factor (GM-CSF), interleukin-1 (IL-1) and tumour necrosis factor alpha (TNF-α) of tumour cells [11].

Ovarian cancer patients suffered more frequently from weakness/vertigo (87.9%) than patients of the cervical or breast cancer group (68.9% and 68.8%). This was similar for the symptom anorexia (81.0% vs 65.5% and 58.8%). A higher percentage of ovarian cancer patients needed parenteral nutrition (48.3% vs 29.1% and 24.1%). Houck et al. [12] also found weakness and anorexia to be the most common symptoms influencing the subjective quality of life of ovarian cancer patients. In general, from our results we received the impression that ovarian cancer patients displayed a worse nutritional condition than cervical or breast cancer patients. This thesis is also supported by other studies [13, 14].

Pain and symptom control was achieved in most of the patients in our study. In 84.7% of all cases patients suffered less from pain or were free of pain at the point of discharge. This shows the high quality and working concept of pain therapy at the palliative care unit at the university hospital of Mannheim. In addition to WHO pain ladder therapy, patients received radiation of the spine or bisphosphonates in case of bone metastases.
metastases. Moreover, if possible, the option of chemotherapy was used for pain reduction.

Our findings, however, show that cervical cancer patients had less pain and greater symptom reduction compared to the patients of the other groups. This does not appear to have been published previously. A few case reports point out that patients of the other groups. This does not appear to have had less pain and greater symptom reduction compared to the other groups. This does not appear to have.

In 76.6% of all cases, patients could be discharged with better general condition and profited from their stay at palliative care unit. The majority of patients were discharged home; a few patients went to a hospice. The survival analysis showed that 74.4% died within the first 6 months (84.4% within 1 year) after the last discharge from the palliative care unit. Median survival from the day of first admission to palliative care unit was 59 days. No comparative publications for gynaecological patients in the palliative care setting exist. Costantini et al. [18] found a median survival of 45 days for breast cancer patients and 35 days for patients with cancer of the female genital tract. Their study was conducted with 589 heterogeneous terminal oncological patients in several different palliative care institutions.

Of the patients in our study, 51.1% died at palliative care unit, 26.7% during their first stay, 24.0% died at home, 13.8% at the hospice and 2.2% elsewhere. More than 50% of the patients at a palliative care unit die at the hospital, although the majority would prefer a domestic environment [19].

The application of chemotherapy during the last stay at the palliative care unit (43 patients) correlated negatively with the overall survival in our study (Gehan-Breslow-Wilcoxon test: p < 0.0013). 17 of 43 patients (39.5%) died within the first 2 weeks after last application. Of course the validity of these results is limited due the retrospective character of this study and the missing randomisation. It is probable that reduced life span was accepted against the benefit of improved quality of life and symptom control – the key targets of palliative care. In fact, the application of palliative chemotherapy at the end of life is becoming more frequent, even when life expectancy is short [20–22]. In this context, the question arises as to whether an ‘overtreatment’ at the end of life is being practised, with perhaps lethal consequences.

Current clinical studies disagree about the benefit of chemotherapy in the palliative setting. While some studies could show advantages for certain cytostatic substances compared to best supportive care [23, 24], and 2 gynaecologically focussed studies [25, 26] even proved a positive influence of chemotherapy on the quality of life, others found only minimal differences in survival for most malignancies [27, 28]. An aim of the present study was to establish prognostic models to aid the decision making for or against cancer therapy. These models also help to reduce the influence of subjective estimates and avoid cancer overtherapy, particular at the end of life, given the actual discussion on this topic.

Patients with terminal cancer and their families frequently request estimations of the length of survival to plan for, and make the best use of, the time that remains [29]. Therefore, the ability to identify factors that can improve prognostic accuracy is important for health professionals in aiding patients and families in their planning. Here, we have analysed the data of patients with breast, ovarian and cervical cancers treated at the palliative care unit of a university hospital since its foundation to assess potential prognostic factors. The date of first admission was defined as the cut-off point for survival analysis as well as the starting point for the assessment of a prognostic impact of symptoms and laboratory values.

Several studies have been conducted to establish palliative prognostic indices or scores [8, 30–35]. Studies have shown that physicians’ survival estimates tend to be overoptimistic and unreliable, especially in terminally ill patients [29, 36, 37]. Therefore, prognostic factors are essential for the survival prediction. Comparable to other studies, we also observed a negative influence of anaemia [37–39], leukocytosis [35, 40–42], low albumin [35, 43, 44], hypercalcaemia [45], levels of LDH [40, 46] and γGT [47, 48]. Anorexia and confusion/cognitive impairment also had a negative impact on the survival time of patients, as in other similar studies [49–52]. In the multivariate Cox regression analysis, all 8 of the above-mentioned prognostic parameters were independently correlated with poor survival time. Based on these unfavourable parameters, 3 patients risk groups were defined: low risk (0–2 factors), intermediate risk (3–5 factors), and high risk (6–8 factors). Median survival time for patients in high-risk group was only 13 days, for intermediate group 61 days, and for low-risk patients 554 days. These factors might help guide treatment decisions with special regard to end-of-life prediction. Patients of the high-risk group benefitted most from timely transfer to a hospice without further cancer therapy.

The large number of available and validated scores, such as the Palliative Prognostic Score [32, 34, 53], that are used for patients with different types of tumour could also be a disadvantage. Theses scores are used assuming that all types of tumour are comparable and patients’ survival is influenced by the same factors. Unfortunately, insufficient data exist to support this assumption and it is possible that different types of cancer cause different problems at the end of life. The statistically validated parameters, found in our study for the first time, should become the subject of future multicentre prospective studies.

In conclusion, we retrospectively analysed a large group of terminally ill patients with gynaecological cancer with respect...
to symptoms and treatment. 8 parameters were identified to be associated with a poor outcome, and patients showing at least 6 or more of these factors had a very limited prognosis. It is hoped that these results may be helpful for individual treatment decisions in patients with advanced gynaecological malignancies.

Online Supplemental Tables

Table 1. Patient characteristics

Table 2. Symptoms on admission (considering all admissions) of terminally ill patients with gynaecological cancer. 497 hospital stays of 225 patients were analyzed

Table 3. Symptoms on first admission of terminally ill patients with gynaecological cancer (n = 225 patients)

Table 4. Medical supportive treatment measures and interventions in terminally ill patients with gynaecological cancer

Table 5. Factors significantly influencing survival of terminally ill patients with gynaecological cancer – results of the univariate analysis. Survival was calculated from the day of first admission to the palliative care unit until death

Table 6. Multivariate Cox proportional hazard analysis of prognostic factors in terminally ill patients with gynaecological cancer; 8 independent factors of poor survival time

All authors indicated no conflicts of interest.

Disclosure Statement

All authors indicated no conflicts of interest.

References


3 Schneider N, Schwartz FW: [High need for improvement and many open questions in health care for palliative patients]. Med Klin (Munich) 2006;101:552–557.


