Cancer Treatment of Severely-III Patients Not Eligible for Chemotherapy

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Abstract. *Background: Despite having disseminated cancer, not all patients are eligible for palliative chemotherapy or targeted therapies. Aim: To study reasons for withholding palliative chemotherapy, to survey which alternatives were offered and to study survival outcomes. Materials and Methods: Medical records of 346 patients with disseminated cancer were collected. Univariate and multivariate statistics were applied. Results: In total, 48% (n=164) of patients were not offered palliative chemotherapy, mainly depending on diagnosis, age and performance status. Instead, palliative radiotherapy (44%) or endocrine treatments (25%) (breast and prostate cancer) were prescribed. The mean survival for these patients was 216 days, with median survival of only 77 days. In the Cox multivariate analysis survival, prospects were better if the patient was ambulatory and living at home at the first consultation (p<0.01), if performance status was acceptable (p<0.01) and if endocrine treatment was an option (p<0.05). Conclusion: The prognosis is quite variable, even in cases where palliative chemotherapy is not an option. A hormone-sensitive tumour and a good performance status are significant factors affecting survival in this patient group.*

For patients with disseminated cancer, the primary goal is good symptom control and quality-of-life, whereas cure is no longer an option. In many cases, prolonged survival is possible to achieve under modern therapy, but as the disease progresses, the positive effects of chemotherapy or targeted drugs diminish. Today, the majority of chemotherapy treatments are given with a palliative intent (1). In a recent study, we found several factors that influence the decision-making with regard to palliative chemotherapy and targeted drugs (2). In accordance with other studies, we found that age, gender, social circumstances, ethnicity and education level were factors of importance (3-8). Some of these have factors also been associated with prolonged survival (9-12).

In our previous study, we found that approximately half of all patients with disseminated disease received palliative chemotherapy, whereas the remainder were referred for best supportive care or standard care elsewhere (2). However, there is no common definition of best supportive care (13, 14), which is problematic in the evaluation of studies where such treatment is compared to palliative chemotherapy treatment (15, 16). Generally, palliative interventions, including issues such as pain and other symptom treatment, psychosocial support as well as other oncological treatments (except for chemotherapy and targeted therapy) are included in the definition of best supportive care. Thus, the patients may for example be administered palliative radiotherapy (17) and bisphosphonate treatment for painful bone metastases. There is growing evidence that many patients with disseminated disease may benefit from a palliative care approach, both regarding quality of life and survival (18, 19). This was elegantly shown in a study of disseminated locally advanced non-small cell lung cancer in 2010 (18), and since then, similar data are being collected for other tumor types.

The aim of the present study was, therefore, to examine which oncological or palliative treatments were offered to patients with disseminated disease, who were not candidates for palliative chemotherapy or targeted therapies.

Materials and Methods

This study was conducted as a single-centre retrospective cohort study at the Department of Oncology at the Karolinska University Hospital. This Department comprises of three different units in the greater Stockholm area and serves the county of Stockholm with a population of about two million inhabitants.

The Regional Oncology Centre office in Stockholm-Gotland helped us identify all patients who had died during 2009 and who had at least one entry in the computerized medical record system generated at the Karolinska Hospital Department of Oncology

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Key Words: Palliative chemotherapy, palliative oncology, supportive care.

Table I. *The proportion of patients receiving palliative chemotherapy (chemotherapy or targeted therapies) in relation to age (date of birth) (n=182 out of the 346 patients).*

Year of birth	Appr. age, years	Chemotherapy given
1920s or earlier	>80	13%
1930s	70-80	50%
1940s	60-70	69%
1950s	50-60	76%
1960s or later	<50	73%

Table II. *Patients for whom primary or secondary chemoresistance was stated as the main reason for refraining from chemotherapy. For breast and prostate cancer, in particular endocrine treatment was preferred in these cases.*

Diagnosis	N=82
Prostate cancer	19 (23%)
Lung cancer	15 (18%)
Upper gastrointestinal cancer	14 (17%)
Renal or urinary bladder cancer	11 (13%)
Breast cancer	8 (10%)
Skin cancer, incl. melanomas	7 (9%)
Other	8 (10%)

Table III. *Reasons for withholding chemotherapy and a list of chosen palliative therapies.*

	Number	Percentage
Reasons for withholding chemotherapy		
Poor performance status	42	26%
Diagnosis (Table II)	82	50%
Patient declined	12	7%
Planned, but patient died before start	18	11%
Missing data	10	6%

during the same period. Manual search identified patients who had died during the months of April and November (representative months for the spring and the autumn, respectively), resulting in 424 patients. These patients were followed from their first contact with the Department (which in some cases was many years before 2009), until their death. Most of these patients were seen regularly by medical staff at one of the oncology clinics. In some cases, there was only documentation of distant consultations or discussions at multidisciplinary conferences. Some patients were treated by specialists in other fields, such as lung medicine or haematology, but a written consultation was made to the Department of Oncology. Patients with benign diagnoses, as well as patients treated with a curative intent who died from causes other than disseminated cancer were excluded, resulting in a cohort of 346 patients. The medical records were reviewed as regards demographic, clinical and treatment-related data. Patients were described as having received chemotherapy if they had received chemotherapy, targeted treatment, or a combination of both. Patients who were not candidates for chemotherapy or targeting drugs were the focus of this study.

Statistics. Descriptive statistics such as mean, medians and proportions were used to describe the data. Group differences were analysed using Student's *T*-test, and if the assumption of normal distribution was not met, we used Mann-Whitney *U*- and Kruskal Wallis tests. Differences in proportions were analysed using Chi^2-test. Multiple logistic regression was performed to determine whether the decision not to prescribe chemotherapy treatment was independently associated with gender, age, education, marital status, presence of under-aged children in the family, or ethnicity. Log-rank (Mantel-Cox) test was performed for univariate survival analysis. A proportional hazards models (Cox regression) was performed for multivariate analysis.

Ethical committee. The study was approved by the regional Ethics Committee (2010/711-31/1).

Results

Characterization of patients not eligible for chemotherapy. Depending on the referral letter, 70% of the patients were seen on personal consultations at the Department, whereas in 30% of the referrals the decision was made without seeing the patient, as the referral text was very informative (for example bedridden patients from other departments where the physician in charge stated a very short expected survival). In 65% of cases the patients were ambulatory, in 31% they were admitted from another hospital department (4% of data were missing). In total, 46% (n=164) of the 346 patients were neither offered palliative chemotherapy, nor targeted therapies with a palliative intent and the probability was related to age (Table I). Compared to those offered palliative chemotherapy, these 164 patients were generally older ($p<0.02$) with no under-aged children ($p<0.001$). A further characterization showed that these patients more often had a low level of education ($p<0.001$), they were of Swedish or European origin (in contrast to non-European origin) ($p<0.05$), they were more often single ($p<0.001$) and male ($p<0.05$). In the multiple regression analysis, age and educational-level remained significant variables, with an odds ratio for age (as a continuous variable) of 1.64 (95% CI 1.06-2.54) for each 10-year increment ($p<0.05$) and an odds ratio of 3.17 (95% CI 1.17-8.58) for a low level of education ($p<0.05$).

There were several stated reasons on the patient charts for not offering chemotherapy. The main reason was that the cancer type was not considered to be sensitive to chemotherapy, alternatively, other treatment options (for example hormonal treatment) were more favourable (Table

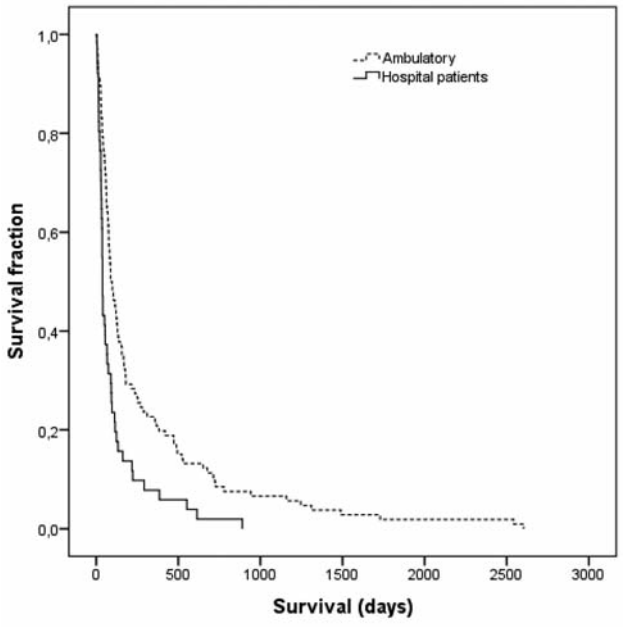

Figure 1. *Patients who were ambulatory had a longer survival compared to patients who were admitted from other hospitals (p<0.001).*

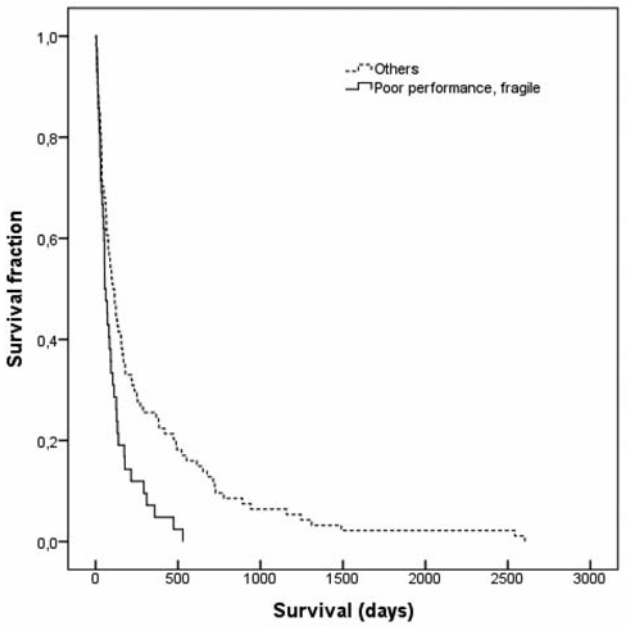

Figure 2. *Those with poor performance status and considered to be in too poor a condition (according to the oncologist) had a shorter survival than those who were not eligible for chemotherapy for other reasons (p=0.002).*

II). Other contributing reasons were low performance status or an explicitly-expressed wish to refrain from chemotherapy treatment (Table III).

Treatment options. When chemotherapy was not a viable option, the most common oncological treatment modality was palliative radiotherapy: 91 radiotherapy treatments, were delivered to 71 patients (some patients received two or more treatments). The most common target was bone metastases (45%), but radiotherapy was also provided as palliation for example for brain metastases (10%), or for symptoms from bladder cancer (8%). In 82% of the cases the patients received one or two treatment series, whereas 18% of the patients were treated with 3-6 series of palliative radiotherapy.

Endocrine treatment was the second most common option. In total, 25% of patients received such treatments, in one and up to five treatment regimens, but generally limited to two regimens (71%). In general, multiple-treatment regimens were related to a diagnosis of metastatic breast cancer. Bisphosphonates were only prescribed to 10% of the patients, despite disseminated disease where bone metastases were frequent.

Predictors for survival. The mean survival from the time of being classified as palliative cases to their death was 216 days (median 77 days), although a few patients with hormone-sensitive tumours survived for up to a few years. Those patients who were ambulatory and living in their own homes, survived longer ($p<0.001$) than those who were admitted from another hospital clinic for the oncological consultation (Figure 1). In cases where the oncologist explicitly noted poor performance status and fragility in the medical records, the mean survival was significantly shorter than for the other patients, with other reasons for refraining from chemotherapy ($p=0.002$) (Figure 2). However, if the patients themselves made the decision not to accept chemotherapy, the survival was not affected. For those patients who received radiotherapy for brain metastases, the mean survival was 119 days (median=74 days), which did not differ from that of the total study population.

Patients suitable for endocrine treatment had significantly better survival prospects ($p<0.001$) than the others, with a mean of 424 days *vs*. 147 days (median=129 *vs*. 67 days) (Figure 3). Even when only considering diagnoses, there was a survival advantage for diagnoses of generally hormone-sensitive breast, prostate, and gynaecological cancer ($p<0.05$). There was also a significant difference when comparing patients who received active oncological treatment (endocrine treatment or radiotherapy) with the others ($p<0.001$). As a last step, proportional hazards models (Cox regression) analysis was performed. Since endocrine treatment and the diagnoses of breast and prostate cancer were strongly correlated, these were not optimal for

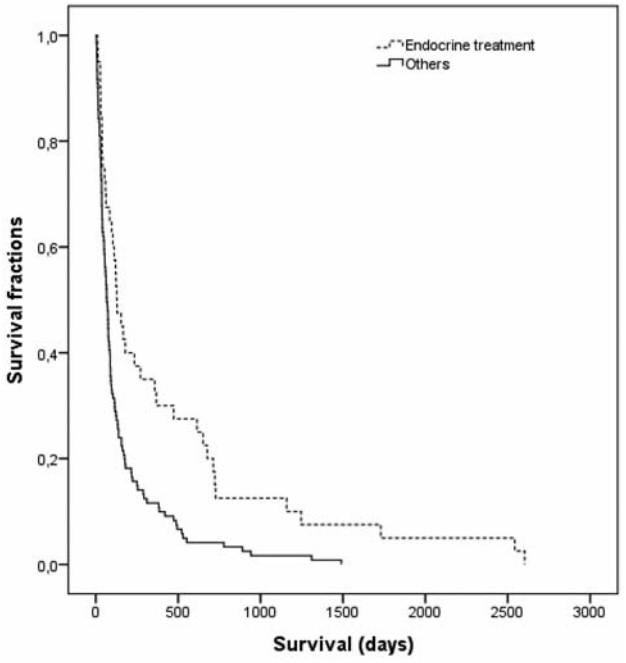

Figure 3. *Patients eligible for endocrine treatment survived longer than those not (p<0.001).*

concomitant inclusion in the same model. Therefore, in the final model, endocrine treatment, performance status/fragility and being ambulatory or not were entered. Longer survival was significantly associated with good performance status, with a hazard ratio of 0.58 (95% CI=0.39-0.85) ($p<0.01$), being ambulatory with a hazard ratio of 0.55 (95% CI=0.37-0.80) ($p<0.01$), and being prescribed endocrine treatment, hazard ratio 0.45 (95% CI=0.44-0.99), ($p<0.05$).

Discussion

In several studies of palliative chemotherapy treatments, best supportive care is used as a comparison group. However, there are no common definitions of what best supportive care should comprise (14) and there are scarce data on which oncological treatment options are offered to those not suitable for palliative chemotherapy or targeted therapies, which was the aim of this study. The patients of this study were those who received best supportive care according to the oncologist's judgement. We were able to demonstrate that about half of all patients with disseminated disease received no chemotherapy or targeted therapy options at all. These patients had poorer survival prospects than those eligible for chemotherapy. As expected, the sub-group of patients for whom endocrine therapy was suitable had better survival, and a fraction of these even responded to second-third- or fourth-line regimens. Patients not eligible for palliative chemotherapy (n=164) were significantly older than patients who were prescribed such treatment. This was an expected finding, as elderly patients are more likely to develop severe side-effects and they have problems with the recovery between treatments (20, 21). In such cases, an endocrine treatment is preferable, if the cancer is hormone-sensitive. As shown, this was the case in elderly patients with breast or prostate cancer, where endocrine treatment was chosen as the main therapy. In general, age was a major factor associated with the choice of therapy.

As expected, palliative radiotherapy was frequently used as it is known to provide effective palliation of pain, dyspnoea and bleeding (22-24). There has even been a consensus in Sweden stating that palliative radiotherapy is used too seldom, especially for painful bone metastases, but nowadays there is a trend towards a more generous use (25). However, the limited survival prospects must be considered when choosing radiotherapy: the median survival was 77 days in this study and for certain treatments, for example radiotherapy for painful bone metastases in prostate cancer, the maximal effect will sometimes occur after 4-5 weeks (26).

Twelve patients declined chemotherapy treatment and there were several personal reasons for this. However, when the decision was based on the patients' expressed wish instead of the assessment of performance status, the survival prospect was not affected. A reasonable interpretation would be that the decision was not based on a subjective feeling of being in the dying phase, but other motives were probably more important. In contrast to this, those patients that were judged as not being suitable for treatment by the oncologist lived for a shorter period than the others, indicating that the decision made by the oncologist was reasonable.

In the clinical setting, the physician made active choices: patients who were likely to respond to hormonal treatment were prescribed endocrine therapy and only patients who had a reasonable performance status were eligible for palliative radiotherapy. Thus, it is not possible to draw a final conclusion on whether survival and the degree of symptom control would have been similar in the patients if the physician had refrained from oncological treatment options and merely used symptomatic treatment with analgesics, corticosteroids and antiemetic-drugs.

In conclusion, patients with cancer who were not offered palliative chemotherapy were in general older, single and male, and had a low educational level. When hormonal treatment was possible, the mean survival was greater than one year (mean=424 days). Patients who were ambulatory at baseline lived longer than those admitted from other hospital departments. Refraining from active treatment was only associated with a poor prognosis when the decision was made by the oncologist, as these patients had a poor performance status. Patients who refrained from chemotherapy based on an active personal choice (for example fear of severe side-effects) did not differ from the whole study group with regard to prognosis.

Acknowledgements

The study was supported by the Swedish Cancer Society (Cancerfonden) and by Stockholm County Council (PickUp grants).

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Received September 5, 2013
Revised October 23, 2013
Accepted October 24, 2013