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ORIGINAL ARTICLE

The role of palliative chemotherapy in hospitalized patients

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ABSTRACT

Background

Hospitalized patients with advanced cancer often have a poor performance status, which is considered a relative contraindication to cytotoxic chemotherapy. We investigated outcomes in hospitalized solid tumour oncology patients who received palliative chemotherapy (PCT).

Methods

With ethics approval, we performed a single-institution chart review of all patients hospitalized on our oncology unit who received PCT between April 2008 and January 2010. Patient demographics, reasons for admission, cancer type, prior therapy, and administered chemotherapy were recorded. The primary endpoint was median survival from date of inpatient chemotherapy until death or last known follow up. We also investigated place of discharge and whether patients received additional therapy.

Results

During the study period, 199 inpatients received PCT. Median age was 61 years; 59% of the patients were women. Most had been admitted with dyspnea (31%) or pain (29%) as the dominant symptom. Common cancers represented were breast (23%), small-cell lung cancer (SCLC, 22%), non-small-cell lung cancer (NSCLC, 16%), and colorectal cancer (9%). Most patients (67%) were receiving first-line chemotherapy. Median overall survival duration was 4.5 months, and the 6-month survival rate was 41%. The longest and shortest survivals were seen in the SCLC and NSCLC groups (7.3 and 2.5 months respectively). Factors significantly associated with shorter survival were baseline hypoalbuminemia and therapy beyond the first line. In this cohort, 77% of patients were discharged home, and 72% received further chemotherapy.

Conclusions

Despite a short median survival, many patients are well enough to be discharged home and to receive further chemotherapy. The development of risk models to predict a higher chance of efficacy will have practical clinical utility.

KEY WORDS

Inpatients, hospitalization, palliative chemotherapy, performance status

1. INTRODUCTION

The life expectancy of patients with advanced cancer is often short, despite continuing improvements in treatment options for many common malignancies such as breast, lung, and colorectal cancer[1–3]. In almost all solid tumours, the presence of distant metastases renders the disease incurable, and therefore systemic therapies are given with the goals of palliating cancer symptoms and prolonging life expectancy.

Decisions about whether patients will accept palliative chemotherapy (PCT) are complex and can vary widely depending on who is being asked to decide[4,5]. In a seminal paper in 1990, Slevin *et al.* reported on the degree of benefit required to accept PCT, observing wide variation in acceptance between patients, nurses, physicians, and members of the public[6]. Guiding decisions and advice in this setting are a number of prognostic factors that can predict the degree of benefit from PCT. One of the most commonly used factors is performance status (PS). Multiple studies have demonstrated that significant clinical benefit (measured by longer survival or improved quality of life) are most commonly seen in patients with Eastern Cooperative Oncology Group (ECOG) PS scores of 0 and 1 (patients that remain relatively asymptomatic and independently functioning). Patients with a PS of 2 experience more limited benefit and a greater risk of toxicity. Most patients with a PS of 3 or 4 are

considered too unwell for PCT, although there are some notable exceptions: for example, small-cell lung cancer (SCLC) is highly chemosensitive and rapidly responsive to therapy[7–10]. Indeed, in 2012, the American Society of Clinical Oncology published their top five recommendations to improve cancer care and reduce costs[11], the first of which says "Do not use cancer-directed therapy for patients with solid tumors who have the following characteristics: low performance status (3 or 4), no benefit from prior evidence-based interventions, not eligible for a clinical trial, and with no strong evidence supporting the clinical value of further anticancer treatment." With that recommendation in mind, tools to identify patients who will not benefit from cytotoxic therapy are clearly useful.

For patients with advanced cancers, physician survival predictions are well-reported to be unreliable and often to overestimate life expectancy, especially in the case of patients near death[12,13]. Nevertheless, treatment of advanced cancer with cytotoxic chemotherapy is increasing and continuing later in life, with a significant proportion of patients receiving chemotherapy within the last 2 weeks of life or being documented to have received "aggressive" end-of-life care[14,15].

Advanced cancer patients who are hospitalized are likely to have a poor PS, and therefore being hospitalized might be considered to be at least a partial contraindication to PCT. The evidence to support PCT in hospitalized patients is scarce. Thus, whether such care has positive effects on survival or quality of life is questionable and merits additional investigation. While recognizing that this measure is subjective, we hypothesized that PCT given to patients admitted to hospital for symptoms of advanced cancer would not result in meaningful clinical benefit. In fact, PCT in this population might often expose sick patients to a high risk of treatment toxicity with only a small chance of modest efficacy. Our institution has a busy inpatient medical oncology service, with approximately 1000 new admissions annually. We therefore performed a single-institution retrospective study to examine outcomes in hospitalized patients receiving PCT.

2. METHODS

With ethics approval from the hospital research ethics board, we conducted a retrospective single-centre chart review to report outcomes from inpatient chemotherapy at our institution between April 2008 and January 2010. From hospital pharmacy records, we identified all advanced solid tumour patients receiving inpatient PCT on the medical oncology unit. Patients receiving radical, curative, neoadjuvant, or adjuvant therapy, and those admitted electively for an inpatient regimen (for example, certain sarcoma protocols) were excluded.

Baseline data on patient demographics and cancer history were collected, together with the reason for hospital admission and baseline laboratory and clinical assessments. With respect to the chemotherapy, data about the type, line, and cycle of therapy were also collected and analyzed. The ECOG PS, where not directly recorded in the clinical notes, was estimated from the clinical assessment at hospital admission. The assumption was made that, to be admitted to hospital, the ECOG PS had to be 2 or greater.

The primary endpoints of the study were overall survival after PCT (defined as the time from the date of inpatient chemotherapy administration until the date of death or last known follow-up), place of discharge from hospital, and whether further chemotherapy was received. Survival curves were generated using the Kaplan–Meier method, and Cox proportional hazards ratios were calculated to compare patient groups. Univariate and multivariate logistic regression was performed to identify factors associated with longer survival, discharge home, and receipt of further chemotherapy. The factors controlled for in the model (in univariate and multivariate analysis) were age, sex, blood work, type of cancer, line of therapy, and reason for hospital admission. All statistical analyses were performed using the SAS statistical software (SAS Institute, Cary, NC, U.S.A.).

3. RESULTS

During the study period, 199 inpatients received PCT (median: 1 cycle; range: 1–5 cycles) for advanced solid tumours. Table I shows baseline demographics for that cohort. Another 104 patients, ineligible for the study and not further reported, received inpatient chemotherapy either in the curative setting or for protocols that require hospitalization, the most common being sarcoma protocols ($n = 67$).

The median age in the study cohort was 61 years (range: 19–88 years), and 59% of the patients were women. The four most common cancers were breast cancer (23%), SCLC (22%), non-small-cell lung cancer (NSCLC, 16%), and colorectal cancer (9%). The most frequent reasons for hospital admission were dyspnea (31%) and pain (29%). At baseline, 25% of the patients had a hemoglobin level below 100 g/L, 36% had leucocytosis, 11% had impaired renal function (defined as creatinine > 120 mmol/L), and 70% were hypoalbuminemic (<30 g/L). Although PS was not routinely recorded, interpretation of the clinical assessments demonstrated that 67% of the patients had an ECOG PS of 2 or 3, and 33% had a PS of 4. With respect to PCT, 67% were receiving first-line chemotherapy, and 48% were receiving their first-ever treatment (that is, cycle 1 of first-line therapy). Single-agent chemotherapy was administered to 63 patients, and 136 patients received combination treatment.

Median survival duration for the entire cohort was 4.5 months [95% confidence interval (CI): 3.2 to

TABLE I Baseline characteristics of the study patients

Characteristic	*Value*
Age (years)	
Median	61
Range)	19–88
Sex [*n* (%)]	
Women	117 (59)
Men	82 (41)
Cancer type [*n* (%)]	
Breast	45 (23)
Small-cell lung	44 (22)
Non-small-cell lung	32 (16)
Colorectal	18 (9)
Other	60 (30)
Estimated ECOG PS [*n* (%)]	
2 or 3	134 (67)
4	65 (33)
Line of therapy [*n* (%)]	
First	133 (67)
Second	28 (14)
Third or subsequent	38 (19)
Blood work at admission [*n* (%)]	
Hemoglobin < 100 g/L	49 (25)
WBC count > 11×10^9/L	72 (36)
Bilirubin > 30 μmol/L	21 (11)
Creatinine > 120 μmol/L	21 (11)
Albumin < 30 g/L	139 (70)
Dominant symptom at admission [*n* (%)]	
Dyspnea	62 (31)
Pain	58 (29)
Other	79 (40)

ECOG PS = Eastern Cooperative Oncology Group performance status; WBC = white blood cell.

5.8 months]. The 3-month, 6-month, and 1-year survival rates were 59%, 41%, and 24% respectively. The longest survival duration was seen in the 44 patients with SCLC (median: 7.3 months; 95% CI: 3.3 to 8.8 months), although the difference was not statistically significant in multivariate analysis ($p = 0.14$). The shortest survival duration was observed in the NSCLC subgroup (median: 2.5 months; 95% CI: 1.1 to 5.0 months). Median survival duration was 4.5 months in both PS subgroups (2–3 and 4). Table II shows median survival duration in all the various subgroups.

Most patients (77%) were discharged home; 17% died during their admission. In univariate analysis, hypoalbuminemia [hazard ratio (HR): 1.43; 95% CI: 1.01 to 2.01; $p = 0.04$] was the only factor associated with being discharged home, but it was nonsignificant in multivariate analysis ($p = 0.14$). Median age of the 33 patients who died while still in hospital was 59 years (range: 24–75 years), and 55% were women. Of the 33 deaths, 7 (21%) occurred in SCLC patients, 5 (15%) in NSCLC patients, and 5 (15%) in patients with pancreatic cancer. Nearly all of those patients (84%) were hypoalbuminemic on admission.

Of the 31 patients (16%) who died within 30 days of receiving PCT, 48% were women. The highest proportion of those deaths occurred in patients with NSCLC (26%), followed by those with breast cancer (19%) and SCLC (16%). Hypoalbuminemia was present on admission in 77% of those patients.

Table III shows factors significantly associated with a shorter survival. In the univariate analysis, those factors were hypoalbuminemia (HR: 1.50; 95% CI: 1.09 to 2.06; $p = 0.01$), and therapy beyond the first line (HR: 1.63; 95% CI: 1.07 to 2.49; $p = 0.02$). In the multivariate analysis, therapy beyond the first line (HR: 2.10; 95% CI: 1.37 to 3.23; $p = 0.0007$) and hypoalbuminemia (HR: 1.52; 95% CI: 1.06 to 2.18; $p = 0.02$) remained significant predictors of shorter survival. In addition, baseline leucocytosis was associated with shorter survival (HR: 1.45; 95% CI: 1.02 to 2.06; $p = 0.03$).

After administration of the inpatient PCT, a large number of patients (72%) went on to receive further systemic therapy; however, no pre-treatment factors were identified in the univariate analysis that were significantly associated with receipt of further chemotherapy.

4. DISCUSSION

In this study, we hypothesized that PCT given to patients admitted to hospital for symptoms of advanced cancer would not result in meaningful clinical benefit. We purposely did not, in this retrospective research, define what might be considered "meaningful clinical benefit," and therefore surrogates of chemotherapy success were selected: for example, whether the patients were well enough to be discharged home or to subsequently receive further therapy. Further, because of the subjectivity of "meaningful clinical benefit," we chose an objective measure as the primary endpoint: overall survival from the time of chemotherapy. Of course, even the surrogate of "further therapy" remains debatable. If the judgment is that the inpatient chemotherapy administration was "aggressive," then it is certainly plausible that the patient and the treating physician will both continue with a similar approach. The rate of response to PCT was not measured because of the heterogeneity of the malignancies treated. The observed median overall survival of 4.5 months was actually longer than we expected, given the initial assumption about the poor overall health of this population. That result might be explained by the high number of patients receiving first-line chemotherapy (67%), of whom many were receiving their first-ever cycle. Therefore, although the 4.5-month survival duration is still short, approximately three quarters of the patients remained

TABLE II Median survival, by subgroup

Patient group	*Proportion of cohort [*n *(%)]*	*Survival (months)*		p *Value (multivariate)*
		Median	*95% CI*	
Overall	199 (100)	4.5	3.2 to 5.8	
Chemotherapy				
First-line	133 (67)	5.1	4.1 to 7.0	<0.001
First-ever (line 1, cycle 1)	95 (48)	4.8	3.0 to 6.4	(1st-line vs. 2nd-line
Not first dose (>line 1, cycle 1)	38 (19)	4.2	2.9 to 5.9	or subsequent)
Cancer type				
Small-cell lung	44 (22)	7.3	3.3 to 8.8	NS
Non-small-cell lung	32 (16)	2.6	1.1 to 5.0	
Breast	45 (23)	4.5	3.2 to 5.8	
ECOG performance status				
2 or 3	134 (67)	4.5	3.2 to 5.8	NS
4	65 (33)	4.5	3.2 to 5.8	
White blood cell count				
$>11\times10^9$/L	72 (36)	4.0	2.4 to 6.0	0.03
$\leq11\times10^9$/L	127 (64)	4.8	3.4 to 6.3	
Albumin				
≥30 g/L	60 (30)	6.4	4.3 to 8.9	0.02
<30 g/L	139 (70)	3.5	2.6 to 5.0	

CI = confidence interval; NS = nonsignificant; ECOG = Eastern Cooperative Oncology Group.

TABLE III Univariate and multivariate analysis of factors associated with shorter survival

Variable	*Univariate analysis*			*Multivariate analysis*		
	HR	*95% CI*	p *Value*	HR	95% CI	p *Value*
Leucocytosis ($>11\times10^9$/L)	1.10	0.81 to 1.49	0.54	1.46	1.03 to 2.06	0.03
Hypoalbuminemia	1.50	1.09 to 2.06	0.01	1.52	1.06 to 2.19	0.02
Line of therapy (2nd and subsequent)	1.47	1.08 to 2.00	0.02	2.10	1.37 to 3.23	<0.01

well enough to be discharged home and to receive further therapy.

Certain cancer types were associated with longer survival, and it was not surprising that the longest survival (7.3 months) was seen in SCLC. Small-cell lung cancer is a disease that often causes significant initial morbidity and that progresses rapidly; urgent admission to hospital for symptom control and initiation of therapy is therefore relatively common. Given that SCLC is particularly chemosensitive, longer survival was expected. The finding that survival duration in the patients with SCLC was not statistically significantly longer than that in the overall cohort might just be a reflection of the overall small number of patients.

In reviewing the recent literature, we found very few data investigating the use of PCT in hospitalized patients. Only one report of a cohort of 92 advanced solid tumour patients hospitalized and treated with PCT could be found[16]. In that group, 74% of the patients (more than in our study) had not received prior therapy, and yet the median overall survival duration was shorter—just 33 days. As in our study, patients who had not received prior therapy experienced significantly longer survival.

Developing tools to guide patients and clinicians about whether to proceed with chemotherapy in this situation would clearly be useful. In our study, the main factors associated with longer survival were the line of therapy and the absence of hypoalbuminemia. The line of therapy was also prognostic in the study by Sanchez–Munoz and colleagues[16], and hypoalbuminemia has previously been reported to be a poor prognostic factor in multiple cancer types[17–19]. Leucocytosis has also previously been reported to be a poor prognostic factor in SCLC[20].

Given the paucity of data in the inpatient setting, clinicians could also look to other clinical scenarios

in which the risk of rapid deterioration is high. For example, patients participating in phase I clinical trials have often been heavily pretreated and could potentially be on the verge of terminal decline. A number of indices have been developed to investigate that scenario. One such index—the Royal Marsden Index (RMI)—was developed in a single-centre retrospective study of 212 patients treated on phase I studies at the Royal Marsden Hospital in the United Kingdom[21]. Using a multivariate analysis, the investigators formulated a 3-point prognostic score to predict 90-day mortality: lactate dehydrogenase (elevated vs. normal), presence of hypoalbuminemia (<35 g/L), and number of metastatic sites (≤2 vs. >2). Of patients with a score of 2 or 3, nearly 90% died within the first 90 days of treatment. The RMI has subsequently been prospectively validated at multiple institutions[22–24]. A variation of the RMI, developed from the same database, has also demonstrated utility with the use of hypoalbuminemia and elevated platelet count (≥400,000/mm^3) as a simple 2-point prognostic score[25]. The Princess Margaret Hospital Index was recently derived for a similar purpose. This 3-point prognostic score consists of ECOG PS (>0), presence of hypoalbuminemia (<35 g/L), and number of metastatic sites (≤2 vs. >2). The Princess Margaret Hospital Index proved to be more sensitive than the RMI (61% vs. 36%) and almost equivalently specific (83% vs. 85%)[26]. We did not have the data to be able to test those tools (specifically, we did not obtain platelet counts or number of metastatic sites).

Other tools in the palliative care environment include the Palliative Performance Scale and the Edmonton Symptom Assessment Scale (ESAS). A low score on the Palliative Performance Scale has been associated with a higher hazard for death in cancer patients in the ambulatory setting[17]. The ESAS is a 9-item patient-rated symptom visual analog scale used to assess the symptoms of patients receiving palliative care. Higher ESAS scores have been reported by at least one third of patients in the last month of life, as shown by a large sample of 10,752 decedents who were included in a province-wide study conducted in Ontario. Hence, the Palliative Performance Scale and the ESAS might both provide clinicians with good clinical markers to help guide decisions about PCT[16]. Management of patients with advanced cancer who are symptomatic enough to require hospitalization should be multidisciplinary. Chemotherapy can certainly be considered and perhaps should be discussed as an option if the patient is chemonaïve, but the involvement of palliative care services should also be considered. Although performed in an outpatient setting, the landmark study by Temel *et al.*[27] demonstrated that early involvement of specialist palliative care services leads to improved quality of life and longer survival in patients with advanced NSCLC.

The type of research reported here has limitations. Because our study was retrospective, the quality of the data available depended on chart documentation, which was variable. In many cases, for example, the functional assessment had to be interpreted subjectively from the chart, which might have led to an incorrect PS classification. We made the assumption that all our patients must have had an ECOG PS of 2 or greater, but that assumption might be inaccurate. If not directly recorded, the PS was estimated from the patient chart, which certainly creates a potential bias. We were not able to determine whether some patients had been in hospital for a relatively uncomplicated problem and had then received chemotherapy as an inpatient because that approach was logistically more feasible than discharging the patient for a treatment already scheduled for the same day. We were able to document discharge to home of a large proportion of the patients, but we were not able to differentiate between those discharged home well and those who might have elected to receive terminal care at home. However, given that the number discharged home was similar to the number receiving further chemotherapy, the latter issue would appear not to have been significant. The foregoing weaknesses can be addressed in a prospective observational cohort study. Also, as noted previously, our study included a heterogeneous group of cancers and of lines and cycles of treatment, which reduced the number of participants in each particular cancer subtype group.

Notably, our study investigated cytotoxic PCT only in the hospitalized population. We did not collect data for patients who received other anticancer therapies—for example, hormonal therapy for metastatic breast cancer or small-molecule biologics for epidermal growth factor receptor mutation-positive lung cancer. Because of the higher efficacy rates and lower toxicity profiles of those drugs, we did not consider their use to be as controversial an area of clinical decision-making.

A prospective study could capture all the prognostic factors identified in other studies (for example, the RMI and the Princess Margaret Hospital index) to investigate whether they are still predictive of 90-day mortality in an inpatient setting. Many groups of cancer patients (poor PS, admitted, heavily pretreated, elderly) might be considered at risk, and whether the prognostic factors that are applicable in one of those groups are valid in another is unknown.

5. CONCLUSIONS

In summary, our retrospective study demonstrates that, although PCT given to hospitalized patients is associated with short survival, most patients remain well enough to be discharged home or to receive further chemotherapy (or both). The presence of hypoalbuminemia and the line of therapy should be taken into consideration when discussing chemotherapy options with hospitalized patients.

6. CONFLICT OF INTEREST DISCLOSURES

The authors have no financial conflicts of interest in relation to this study, which was performed without funding.

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