Original Article

PALLIATIVE MEDICINE

Palliative Medicine
2015, Vol. 29(9) 826–833

DOI: 10.1177/0269216315583031
pmj.sagepub.com
SAGE

Acute symptomatic complications among patients with advanced cancer admitted to acute palliative care units: A prospective observational study

David Hui[1], Renata dos Santos[2], Suresh Reddy[1], Maria Salete de Angelis Nascimento[2], Donna S Zhukovsky[1], Carlos Eduardo Paiva[2], Shalini Dalal[2], Everaldo Donizeti Costa[2], Paul Walker[1], Heloisa Helena Scapulatempo[2], Rony Dev[1], Camila Souza Crovador[2], Maxine De La Cruz[1] and Eduardo Bruera[1]

Abstract

Background: Limited information is available on the symptomatic complications that occur in the last days of life.

Aim: We documented the frequency, clinical course, and survival for 25 symptomatic complications among patients admitted to acute palliative care units.

Design: Prospective longitudinal observational study.

Measurements: Their attending physician completed a daily structured assessment of symptomatic complications from admission to discharge or death.

Setting/participants: We enrolled consecutive advanced cancer patients admitted to acute palliative care units at MD Anderson Cancer Center, USA, and Barretos Cancer Hospital, Brazil.

Results: A total of 352 patients were enrolled (MD Anderson Cancer Center = 151, Barretos Cancer Hospital = 201). Delirium, pneumonia, and bowel obstruction were the most common complications, occurring in 43%, 20%, and 16% of patients on admission, and 70%, 46%, and 35% during the entire acute palliative care unit stay, respectively. Symptomatic improvement for delirium (36/246, 15%), pneumonia (52/161, 32%), and bowel obstruction (41/124, 33%) was low. Survival analysis revealed that delirium ($p < 0.001$), pneumonia ($p = 0.003$), peritonitis ($p = 0.03$), metabolic acidosis ($p < 0.001$), and upper gastrointestinal bleed ($p = 0.03$) were associated with worse survival. Greater number of symptomatic complications on admission was also associated with poorer survival ($p < 0.001$).

Conclusion: Symptomatic complications were common in cancer patients admitted to acute palliative care units, often do not resolve completely, and were associated with a poor prognosis despite active medical management.

Keywords

Complications, hemorrhage, infection, intestinal obstruction, morbidity, neoplasms, palliative care

What is already known about the topic?

- Symptomatic complications often increase as patients approach the end of life.
- There is a paucity of published literature on the acute complications that occur in cancer patients in the last days of life, their symptomatic impact, and outcome.

[1]Department of Palliative Care & Rehabilitation Medicine, University of Texas MD Anderson Cancer Center, Houston, TX, USA
[2]Department of Palliative Care, Barretos Cancer Hospital, Barretos, Brazil

Corresponding author:
David Hui, Department of Palliative Care & Rehabilitation Medicine, University of Texas MD Anderson Cancer Center, Unit 1414, 1515 Holcombe Boulevard, Houston, TX 77030, USA.
Email: dhui@mdanderson.org

What this paper adds?

- In this prospective observational study, we systemically examined the frequency, clinical course, and survival for 25 symptomatic complications among cancer patients admitted to acute palliative care units.

Implications for practice?

- Symptomatic complications were common in cancer patients admitted to acute palliative care units, often do not resolve completely, and were associated with a poor prognosis despite active medical management.
- Given the poor survival associated with these complications, we recommend a prognosis-based approach to medical decision making in the acute palliative care unit, carefully balancing the risks and benefits for investigations and therapies.

Introduction

As cancer patients approach the last few months of life, they often experience an increased number of complications, associated with a greater number of emergency room visits and hospitalizations.[1,2] Barbera et al.[3] reported that some of the common reasons for patients to visit emergency rooms in the last 6 months of life were pain (7%), pneumonia (4%), obstruction (2%), and delirium (2%). In a retrospective case series, Herrinton et al.[4] documented the complications in ovarian cancer patients in the last 6 months of life and reported that ascites, bowel obstruction, pleural effusion, and bladder obstruction were among the most common complications.

In the last weeks to days of life, acute complications are particularly common, leading to multiple symptoms and rapid functional decline.[5] Many patients require hospitalization, with approximately one in three cancer patients dying in hospitals.[6–8] In tertiary care hospitals, patients may be admitted to acute palliative care units (APCUs) under the care of an interprofessional palliative care team.[9] APCUs currently exist in approximately 20% of larger hospitals in the United States[10,11] and are also available in many other European and Latin American countries.[12,13] These specialized inpatient units provide intensive symptom control and psychosocial support, manage acute complications, and facilitate discharge planning and transition to end-of-life care.[14–16] A recent survey of bereaved family members suggested that the end-of-life care at APCUs was perceived to be superior to palliative care consultation team or usual care.[17,18]

With the exception of infections and antibiotics use,[19–24] much is not known about the symptomatic complications that occur in the last weeks to days of life in regard to their frequency, clinical course, and prognostic significance.

A better understanding of these symptomatic complications and their outcomes may facilitate clinical decision making and allow us to optimize patient care. In this study, we documented the frequency, clinical course, and survival for 25 symptomatic complications in patients with advanced cancer admitted to APCUs at two tertiary care cancer centers.

Patients and methods

Study setting and criteria

The Investigating the Process of Dying study is a prospective observational study that systematically documented the clinical signs and symptoms in the last days of life, which has been reported elsewhere.[25–28] This article focuses on physician assessments of symptomatic complications. Briefly, consecutive advanced cancer patients who were admitted to the APCUs at MD Anderson Cancer Center (MDACC, Houston, TX, USA) between 5 April and 6 July 2010, and at Barretos Cancer Hospital (BCH, Barretos, Brazil) between 27 January and 1 June 2011 were enrolled onto this study. This non-interventional study was approved by the Institutional Review Boards at both hospitals with waiver of informed consent for patient participation because we only collected data based on clinicians' observations. All physicians who participated in this study provided written informed consent in the local language (i.e. English or Portuguese) prior to patient enrollment.

Both APCUs are situated within tertiary care cancer centers and provide comprehensive symptom management and psychosocial support by an interdisciplinary team, transition of care, and discharge planning.[10,16] Both APCUs routinely assess symptoms using standardized questionnaires such as the Edmonton Symptom Assessment Scale[29] and the Memorial Delirium Assessment Scale,[30] and treat acute complications that occur with full access to diagnostic and therapeutic measures, such as computed tomography, intravenous antibiotics, supplemental oxygen, and thoracentesis. Treatment decisions are made after assessing the risks and benefits, incorporating the goals of care, prognostic information, and symptom distress. The historical APCU mortality rate was 30% for MDACC and 60% for Brazil. This difference may be attributed to differences in reimbursement policies of two countries, in which patients in Brazil were able to spend the last days of their lives in the hospital.

Data collection

Palliative care physicians attending the APCUs prospectively documented the frequencies of 25 symptomatic

complications on a daily basis for all patients from APCU admission to death or discharge based on all available bedside clinical, laboratory, and radiologic investigations. These symptomatic complications were defined a priori by the research team based on their relative frequencies and clinical relevance and included bowel obstruction, bowel perforation, cerebral hemorrhage, delirium, fracture(s), heart failure, hemoptysis, hypercalcemia, hyperkalemia, hypernatremia, hyponatremia, ischemic stroke, lower gastrointestinal (GI) bleed, metabolic acidosis, myocardial infarction, peritonitis, pneumonia, pressure ulcer, pulmonary embolism, renal failure, retroperitoneal bleed, sepsis, tamponade, upper GI bleed, and urinary tract infection. For each complication, the attending palliative care specialist answered the question "Is this complication contributing to symptom burden?" ("No," "Possibly," or "Probably") using a standardized checklist. We decided to only collect data on symptomatic complications instead of any acute complication because (1) symptomatic complications were of particular clinical relevance in the palliative care setting, (2) asymptomatic complications were often difficult to document accurately when screening investigations were not routinely conducted given the frailty of our patient population, and (3) it is not practical to determine whether a complication has completely resolved in a patient who has only days to weeks of survival because of the many competing events.

Standardized data collection forms were used for documenting the complications and were completed after daily patient care rounds. All palliative care physicians completed an orientation on the study objectives and data collection process. We reviewed the collected data every day to ensure they were complete and logical. On rare occasions in which data were missing or inconsistent with clinical chart, the research team approached the attending physician in person to seek immediate feedback and clarification as part of the quality control process. All data collection forms used in Brazil were translated into Portuguese and then back-translated. The two institutions had weekly video conference to discuss the research process and conducted site visits mutually.

Statistical analysis

Our pre-planned sample size was a combined total of 200 deaths in the two study sites as stated previously.[25] This analysis was planned based on the combined data a priori because of the similar patterns of practice in the two APCUs, and that the pooled data will provide a large sample size for analysis while increasing the generalizability of our findings.

We summarized the baseline demographics with descriptive statistics. This analysis was based on the combined data from both study sites, given that the pattern of clinical practice and frequency of complications were comparable. We determined the frequency of each complication at the time of APCU admission and also during the entire admission. For analysis purposes, we dichotomized all responses for each (symptomatic complication absent = "No," present = "Possibly" or "Probably"). For example, symptomatic hypercalcemia would be coded as absent if the patient had a normal corrected serum calcium or if it was elevated but the patient did not have any symptoms related to hypercalcemia (e.g. delirium). It would be coded as present if the patient had some symptoms that could be attributed to hypercalcemia. We used the Mann–Whitney test to compare the number of symptomatic complications between patients who were discharged alive and those who died in the APCUs.

We also determined the resolution of symptoms related to each complication among patients who had the symptomatic complication documented at least once during the APCU stay. We defined a symptomatic complication as resolved if it occurred but was not documented for at least 3 days prior to death or discharge.

Overall survival was calculated from the time of APCU admission to death or last follow-up. We compared the survival between patients with and without each symptomatic complication at the time of APCU admission using the Kaplan–Meier method and the log rank test.

The Statistical Analysis System (SAS version 9.2; SAS Institute, Cary, NC, USA) was used for statistical analysis. A p-value of <0.05 was considered significant.

Results

Patient characteristics

A total of 357 patients were included in this study. Five patients were admitted to APCUs in the afternoon and then died the next morning before the attending physician was able to see them and were excluded from the analysis. As projected, 52 of 151 (34%) MDACC and 147 of 201 (73%) BCH patients died in the APCU. The patient characteristics are shown in Table 1. BCH had more female patients (51% vs 37%, $p = 0.009$), Hispanics (100% vs 18%, $p < 0.001$), Christians (98% vs 86%, $p < 0.001$), and GI cancer (35% vs 20%, $p < 0.001$) than MDACC.

Among the 40 physicians who documented the complications, the mean age was 35 years, 13 (33%) were female, 31 (78%) were Hispanic, and the median duration of postgraduate clinical experience was 5 years (interquartile range 4–10 years).

Frequency of symptomatic complications

The frequency of occurrence for each complication is shown in Table 2. Delirium, pneumonia, and bowel obstruction were the most common symptomatic complications, occurring in 43%, 20%, and 16% of patients on

Table 1. Patient characteristics.

Characteristics	All patients, $N = 352$ (%)[a]
Age, average (range)	57 (18–88)
Female sex	193 (55)
Ethnicity	
White	98 (28)
Black	21 (6)
Hispanic	228 (65)
Others	5 (1)
Christian religion	325 (93)
Married	205 (59)
Cancer	
Breast	40 (11)
Gastrointestinal	100 (28)
Genitourinary	36 (10)
Gynecological	40 (11)
Head and neck	26 (7)
Hematological	17 (5)
Others	43 (12)
Respiratory	50 (14)
Co-morbidities	
Emphysema	16 (5)
Heart failure	17 (5)
Coronary artery disease	13 (4)
Stroke	7 (2)
Chronic kidney disease	5 (1)
Diabetes	50 (14)
Duration of palliative care unit admission, median days (interquartile range)	6 (4–9)

[a]Unless otherwise specified.

admission, and 70%, 46%, and 36% during the entire APCU stay, respectively.

Other than bowel obstruction (MDACC vs BCH: 21% vs 47%, $p < 0.001$), hypercalcemia (8% vs 38%, $p < 0.001$), pneumonia (58% vs 37%, $p < 0.001$), and urinary tract infections (9% vs 41%, $p < 0.001$), the frequency of complications did not differ by more than 20% between the two sites.

Figure 1(a) shows the number of symptomatic complications upon initial APCU admission and during APCU stay. Patients who died in the APCU had a slightly higher number of symptomatic complications on APCU admission compared to patients who were discharged alive (median 2 vs 2; $p = 0.003$), and also a higher number of symptomatic complications documented during the entire APCU stay (median 5 vs 4; $p = 0.03$).

Resolution of symptomatic complications

Table 2 shows that a majority of the symptomatic complications remained until the time of discharge or death. Despite antibiotic therapy, symptoms from pneumonia, urinary tract infections, and sepsis improved in only 52 of 161 (32%), 42 of 95 (44%), and 34 of 88 (39%) patients, respectively. Delirium symptoms were least likely to resolve (36/246, 15%).

Survival associated with symptomatic complications

The overall median survival for our cohort was 10 days (95% confidence interval 8–12 days). Table 3 shows the overall survival according to the presence or absence of each complication. Figure 2 shows the survival curves for symptomatic complications that were associated with a poorer survival. Higher number of symptomatic complications on APCU admission was associated with worse overall survival (Figure 2).

Discussion

In this study of patients with advanced cancer admitted to APCUs, we found that symptomatic complications were common, often do not completely resolve, and were associated with a poor prognosis despite active medical management. Our findings may facilitate clinical decision making for acute ill hospitalized patients and highlight the need for further research to manage these complications.

To our knowledge, this is the first study to prospectively document a wide array of symptomatic complications in consecutive patients admitted to APCUs. Importantly, this study focused on symptom-directed diagnoses rather than whether an acute complication was present or not. Thus, complications that were asymptomatic were not considered (e.g. subclinical pneumonia or hypernatremia). One of the strengths of this prospective study is that we utilized experienced palliative care specialists who were involved in the day-to-day management of these patients for data capture. By systematically documenting the complications in a serial fashion, we were able to determine their relative frequencies and clinical course. Despite the known differences in patient characteristics between the two study sites, the complication frequencies were comparable.

We found that symptomatic delirium, pneumonia, and bowel obstruction occurred most frequently, followed by urinary tract infections, sepsis, hypercalcemia, and pressure ulcers. The frequency of infections in our cohort is comparable to others,[19,31,32] providing support for our findings. The remaining conditions were reported in less than 20% of patients. Patients had a median of two symptomatic complications documented on admission, which increased to five during their APCU stay as a result of increased duration of observation and diagnostic investigations.

Unfortunately, many of these complications remained symptomatic despite active interventions. Our rates of symptom resolution ranged from 67% for tamponade to

Table 2. Frequency and resolution for 25 symptomatic complications in acute palliative care units ($N = 352$).

Symptomatic complication	Frequency on APCU admission, *N* (%)	Frequency during the entire APCU stay, *N* (%)[a]	Symptomatic resolution, *n*/*N* (%)[b]
Bowel obstruction	57 (16)	124 (35)	41/124 (33)
Bowel perforation	9 (3)	45 (13)	26/45 (58)
Cerebral hemorrhage	6 (2)	40 (11)	21/40 (53)
Delirium	150 (43)	246 (70)	36/246 (15)
Fracture(s)	9 (3)	30 (9)	13/30 (43)
Heart failure	25 (7)	53 (15)	19/53 (36)
Hemoptysis	4 (1)	26 (7)	17/26 (65)
Hypercalcemia	41 (12)	87 (25)	38/87 (44)
Hyperkalemia	9 (3)	25 (7)	12/25 (48)
Hypernatremia	5 (1)	16 (5)	9/16 (56)
Hyponatremia	29 (8)	67 (19)	29/67 (43)
Ischemic stroke	8 (2)	23 (7)	8/23 (35)
Lower GI bleed	17 (5)	47 (13)	20/47 (43)
Metabolic acidosis	17 (5)	49 (14)	18/49 (37)
Myocardial infarction	2 (1)	16 (5)	6/16 (38)
Peritonitis	9 (3)	35 (10)	14/35 (40)
Pneumonia	70 (20)	161 (46)	52/161 (32)
Pressure ulcer	25 (7)	73 (21)	29/73 (40)
Pulmonary embolism	26 (7)	69 (20)	32/69 (46)
Renal failure	32 (9)	56 (16)	19/56 (34)
Retroperitoneal bleed	2 (1)	8 (2)	3/8 (38)
Sepsis	29 (8)	88 (25)	34/88 (39)
Tamponade	3 (1)	9 (3)	6/9 (67)
Upper GI bleed	8 (2)	25 (7)	13/25 (52)
Urinary tract infection	32 (9)	95 (27)	42/95 (44)

APCU: acute palliative care unit; GI: gastrointestinal.

[a]Coded as present if the patient had a symptomatic complication documented on any of the APCU days based on the daily forms completed by APCU physicians.

[b]Reversibility was defined in this study as the absence of symptoms from a complication in the last 3 days of APCU stay (numerator), regardless of whether the patient died or not. The denominator was based on the frequency during the entire APCU stay.

15% for delirium. The relatively high rates of improvement for tamponade were likely because this acute life-threatening complication often triggered immediate pericardiocentesis, which could improve symptoms effectively. In contrast, the low rates of resolution for delirium were likely related to the pathophysiologic changes in the last days of life.[33,34] There is currently a paucity of clinical trials in delirium among cancer patients.[35] Further research is urgently needed to optimize delirium management in APCU patients. Reassuringly, our symptomatic response for pneumonia (32%) and urinary tract infections (44%) is generally consistent with the literature, which has been reported to be between 15% and 62%.[20,21,23,32,36,37]

We found that many symptomatic complications were associated with poorer survival, even in a relatively homogenous population with a short survival. This is not surprising given that these complications were serious, often not easily reversible, and patients were extremely frail. The prognostic significance for several complications, such as pneumonia[38] and hypercalcemia,[39] has been documented previously. Our study further highlights that patients with a higher number of complications on admission were likely to do worse.

Our findings have clinical implications. Because symptomatic complications such as delirium, pneumonia, and bowel obstruction occur commonly in the last days of life and are associated with significant morbidity and mortality, we hypothesize that preventative measures, close surveillance, and prompt initiation of interventions may improve clinical outcomes. Our data also revealed that many of these symptomatic complications were not reversible despite intensive interventions in APCUs by specialized palliative care teams, suggesting that it is not always possible to die without symptoms among patients who required an APCU admission. This information may facilitate the complex decision-making processes surrounding initiating, withholding, and withdrawing treatments for complications in the APCU setting.

Our study has several limitations. First, we only inquired about 25 complications to limit study burden. Future studies may need to examine other symptomatic complications such as pleural effusion, ascites, urinary

Table 3. Overall survival by 23 symptomatic complications on acute palliative care unit admission[a].

Symptomatic complication	Median survival (95% CI) when complication present on admission	Median survival (95% CI) when complication absent on admission	*p*-Value
Bowel obstruction	8 (5–11)	11 (9–13)	0.29
Bowel perforation	19 (0–57)	10 (8–12)	0.97
Cerebral hemorrhage	7 (0–15)	10 (8–12)	0.58
Delirium	7 (6–8)	17 (12–23)	<0.001
Fracture(s)	33 (8–58)	10 (8–12)	0.38
Heart failure	7 (4–10)	11 (9–13)	0.13
Hemoptysis	9 (0–19)	10 (8–12)	0.62
Hypercalcemia	8 (3–13)	10 (8–12)	0.06
Hyperkalemia	6 (3–9)	10 (8–12)	0.97
Hypernatremia	7 (3–11)	10 (8–12)	0.68
Hyponatremia	8 (4–12)	11 (9–13)	0.09
Ischemic stroke	8 (0–20)	10 (8–12)	0.62
Lower GI bleed	14 (0–29)	10 (8–12)	0.58
Metabolic acidosis	5 (4–6)	11 (9–13)	<0.001
Peritonitis	4 (1–7)	10 (8–12)	0.03
Pneumonia	8 (5–11)	11 (9–13)	0.003
Pressure ulcer	7 (5–9)	10 (8–12)	0.16
Pulmonary embolism	9 (3–15)	10 (9–12)	0.45
Renal failure	7 (1–13)	10 (8–12)	0.34
Sepsis	8 (4–12)	10 (8–12)	0.18
Tamponade	8 (0–18)	10 (8–12)	0.11
Upper GI bleed	6 (5–7)	10 (8–12)	0.03
Urinary tract infection	9 (5–13)	10 (8–12)	0.65

CI: confidence interval; GI: gastrointestinal.
[a]Symptomatic myocardial infarction and retroperitoneal bleed were documented in three and one patients, respectively. The small number of patients precluded survival analysis.

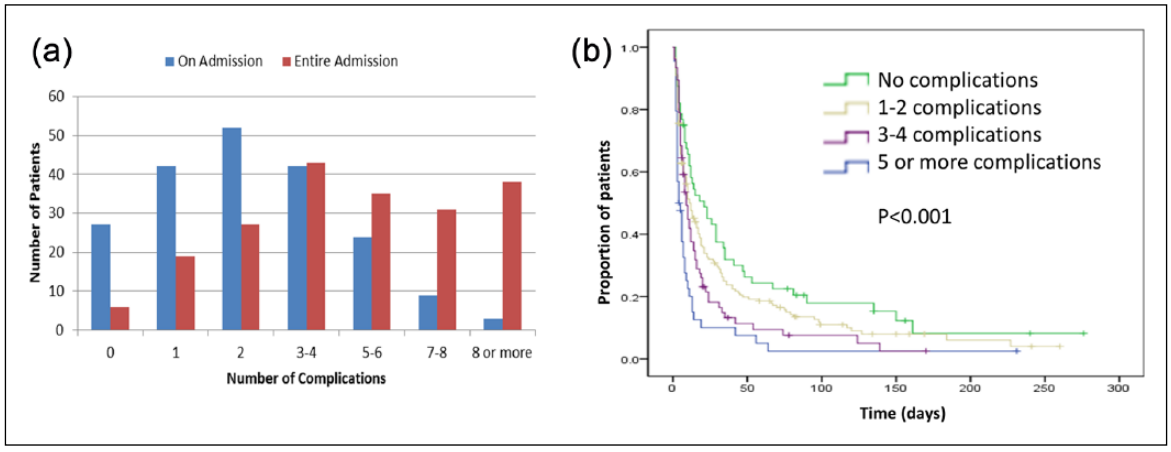

Figure 1. Number of symptomatic complications in acute palliative care units (APCU): (a) the number of symptomatic complications on APCU admission and during the entire stay are plotted and (b) the number of symptomatic complications on APCU admission was associated with worse survival.

retention, and dehydration. Second, we did not report the intensity of symptoms related to each complication. Although this study captured serial symptom data concurrently, attribution was challenging because symptom expression is related to numerous inter-related factors. Third, we did not capture the specific treatments for each complication, partly because of the diversity of interventions and the complex decision-making process. It is the policy of both APCUs to treat all symptomatic complications where possible, with the goals of reducing distress,

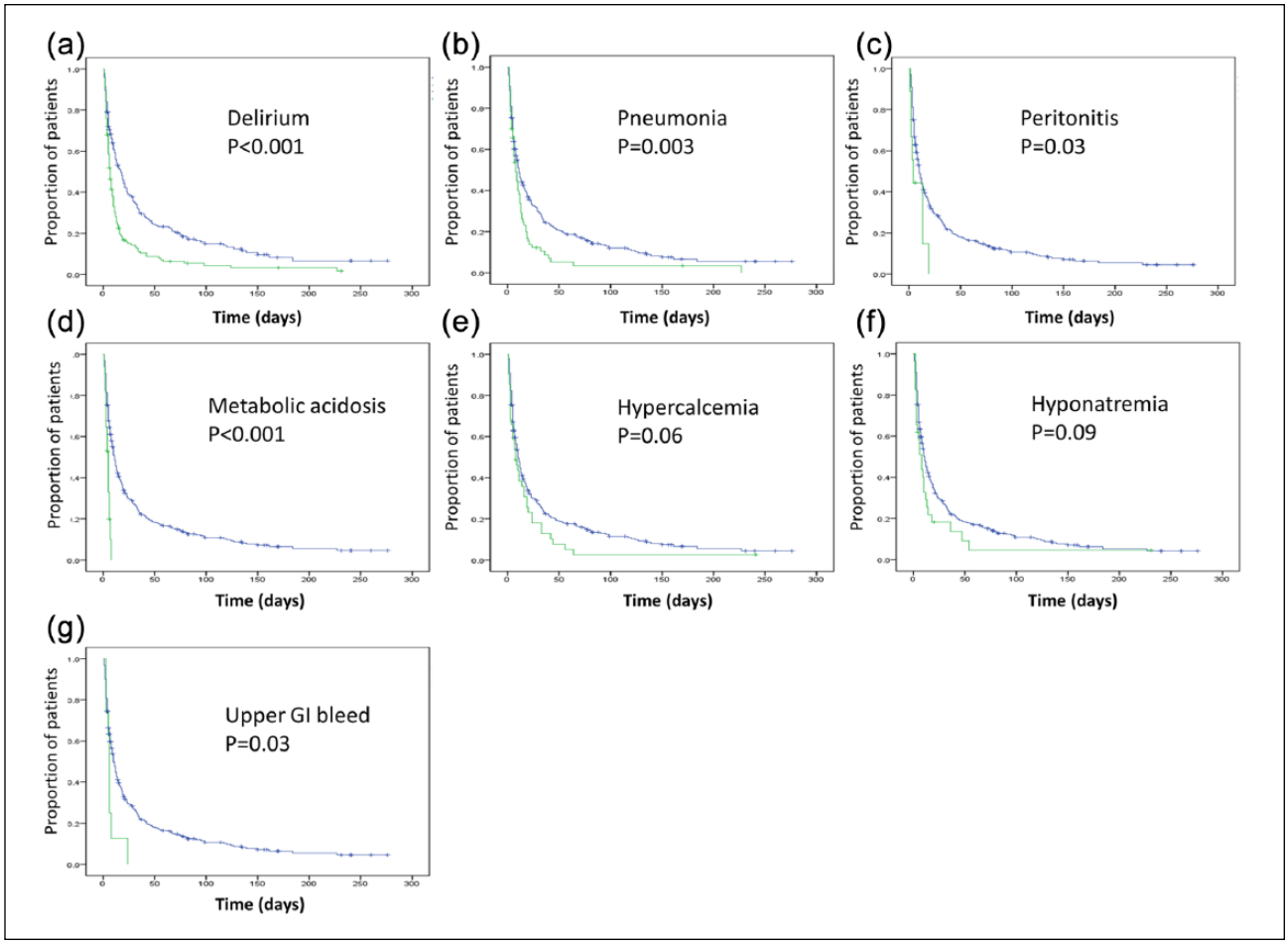

Figure 2. Symptomatic complications associated with shorter survival. Survival was poorer for patients with the following complications on admission (green curves): (a) delirium, (b) pneumonia, (c) peritonitis, (d) metabolic acidosis, (e) hypercalcemia (not statistically significant), (f) hyponatremia (not statistically significant), and (g) upper GI bleed.

restoring function, and facilitating a safe discharge. Fourth, the inter-rater reliability was not examined. We relied on experienced palliative care physicians to document their clinical judgment. Further research is needed to examine the inter-rater agreement among physicians. Fifth, the daily monitoring of complications may contribute to surveillance bias, resulting in a higher rate of complication than in routine clinical practice. Finally, some of the individual complications occurred infrequently. Thus, our relatively small sample size may not have enough power to detect a true difference in survival.

In summary, symptomatic complications were common among patients admitted to APCUs. Clinicians, patients, and families should be made aware that many of these complications may not resolve despite active medical management. Given the poor survival associated with these complications, we recommend a prognosis-based approach to medical decision making in the APCU, carefully balancing the risks and benefits for investigations and therapies.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

Funding

This work was supported, in part, by National Institutes of Health grants RO1NR010162-01A1, RO1CA122292-01, and RO1CA 124481-01 (to E.B.). This study was also supported by the MD Anderson Cancer Center Support Grant (CA 016672) and an institutional startup grant #18075582 (to D.H.).

References

1. Rosenwax LK, McNamara BA, Murray K, et al. Hospital and emergency department use in the last year of life: a baseline for future modifications to end-of-life care. *Med J Australia* 2011; 194: 570–573.
2. Von Gruenigen V, Daly B, Gibbons H, et al. Indicators of survival duration in ovarian cancer and implications for aggressiveness of care. *Cancer* 2008; 112: 2221–2227.
3. Barbera L, Taylor C and Dudgeon D. Why do patients with cancer visit the emergency department near the end of life? *CMAJ* 2010; 182: 563–568.

4. Herrinton LJ, Neslund-Dudas C, Rolnick SJ, et al. Complications at the end of life in ovarian cancer. *J Pain Symptom Manag* 2007; 34: 237–243.
5. Seow H, Barbera L, Sutradhar R, et al. Trajectory of performance status and symptom scores for patients with cancer during the last six months of life. *J Clin Oncol* 2011; 29: 1151–1158.
6. Hui D, Didwaniya N, Vidal M, et al. Quality of end-of-life care in patients with hematologic malignancies: a retrospective cohort study. *Cancer* 2014; 120: 1572–1578.
7. Group TDAW. *Dartmouth Atlas of Health Care*. The Dartmouth Institute for Health Policy and Clinical Practice, 2012. Available at: http://www.dartmouthatlas.org/ (accesses 23 October 2012).
8. Wennberg JE, Fisher ES, Stukel TA, et al. Use of hospitals, physician visits, and hospice care during last six months of life among cohorts loyal to highly respected hospitals in the United States. *BMJ* 2004; 328: Article 607.
9. Lagman R, Rivera N, Walsh D, et al. Acute inpatient palliative medicine in a cancer center: clinical problems and medical interventions—a prospective study. *Am J Hosp Palliat Care* 2007; 24: 20–28.
10. Hui D, Elsayem A, De la Cruz M, et al. Availability and integration of palliative care at US cancer centers. *JAMA* 2010; 303: 1054–1061.
11. Billings JA and Pantilat S. Survey of palliative care programs in United States teaching hospitals. *J Palliat Med* 2001; 4: 309–314.
12. Centeno C, Lynch T, Donea O, et al. *EAPC Atlas of Palliative Care in Europe 2013—full edition*. Milano: European Association for Palliative Care, 2013. Available at: http://dadun.unav.edu/handle/10171/29291?locale=en (accessed 12 February 2015).
13. Pastrana T, Eisenchlas J, Centeno C, et al. Status of palliative care in Latin America: looking through the Latin America Atlas of Palliative Care. *Curr Opin Support Palliat Care* 2013; 7: 411–416.
14. Arthur J, Hui D, Reddy S, et al. Till death do us part: getting married at the end of life. *J Pain Symptom Manag* 2012; 44: 466–470.
15. Alonso-Babarro A, Bruera E, Varela-Cerdeira M, et al. Can this patient be discharged home? Factors associated with at-home death among patients with cancer. *J Clin Oncol* 2011; 29: 1159–1167.
16. Hui D, Elsayem A, Li Z, et al. Antineoplastic therapy use in patients with advanced cancer admitted to an acute palliative care unit at a comprehensive cancer center: a simultaneous care model. *Cancer* 2010; 116: 2036–2043.
17. Casarett D, Johnson M, Smith D, et al. The optimal delivery of palliative care: a national comparison of the outcomes of consultation teams vs inpatient units. *Arch Intern Med* 2011; 171: 649–655.
18. Bruera E and Hui D. Palliative care units: the best option for the most distressed. *Arch Intern Med* 2011; 171: 1601; author reply 1601–1602.
19. Pereira J, Watanabe S and Wolch G. A retrospective review of the frequency of infections and patterns of antibiotic utilization on a palliative care unit. *J Pain Symptom Manag* 1998; 16: 374–381.
20. Vitetta L, Kenner D and Sali A. Bacterial infections in terminally ill hospice patients. *J Pain Symptom Manag* 2000; 20: 326–334.
21. Chen LK, Chou YC, Hsu PS, et al. Antibiotic prescription for fever episodes in hospice patients. *Support Care Cancer* 2002; 10: 538–541.
22. Oneschuk D, Fainsinger R and Demoissac D. Antibiotic use in the last week of life in three different palliative care settings. *J Palliat Care* 2002; 18: 25–28.
23. Clayton J, Fardell B, Hutton-Potts J, et al. Parenteral antibiotics in a palliative care unit: prospective analysis of current practice. *Palliat Med* 2003; 17: 44–48.
24. Lam PT, Chan KS, Tse CY, et al. Retrospective analysis of antibiotic use and survival in advanced cancer patients with infections. *J Pain Symptom Manag* 2005; 30: 536–543.
25. Hui D, Dos Santos R, Chisholm G, et al. Clinical signs of impending death in cancer patients. *Oncologist* 2014; 19: 681–687.
26. Bruera S, Chisholm G, Santos RD, et al. Variations in vital signs in the last days of life in patients with advanced cancer. *J Pain Symptom Manag* 2014; 48: 510–517.
27. Hui D, Dos Santos R, Chisholm G, et al. Bedside clinical signs associated with impending death in patients with advanced cancer: preliminary findings. *Cancer* 2015; 121: 960–967.
28. Hui D, Dos Santos R, Chisholm G, et al. Symptom expression in the last seven days of life among cancer patients admitted to acute palliative care units. *J Pain Symptom Manag*. Epub ahead of print 19 September 2014. DOI: 10.1016/j.jpainsymman.2014.09.003.
29. Bruera E, Kuehn N, Miller MJ, et al. The Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients. *J Palliat Care* 1991; 7: 6–9.
30. Breitbart W, Rosenfeld B, Roth A, et al. The Memorial Delirium Assessment Scale. *J Pain Symptom Manag* 1997; 13: 128–137.
31. Nagy-Agren S and Haley H. Management of infections in palliative care patients with advanced cancer. *J Pain Symptom Manag* 2002; 24: 64–70.
32. Oh DY, Kim JH, Kim DW, et al. Antibiotic use during the last days of life in cancer patients. *Eur J Cancer Care (Engl)* 2006; 15: 74–79.
33. Hui D, De La Cruz M and Bruera E. Palliative care for delirium in patients in the last weeks of life: the final frontier. *J Palliat Care* 2014; 30: 259–264.
34. Shin SH, Hui D, Chisholm G, et al. Frequency and outcome of neuroleptic rotation in the management of delirium in patients with advanced cancer. *Cancer Res Treat*. Epub ahead of print 24 November 2014. DOI: 10.4143/crt.2013.229.
35. Hui D, Bush SH, Gallo LE, et al. Neuroleptic dose in the management of delirium in patients with advanced cancer. *J Pain Symptom Manag* 2010; 39: 186–196.
36. White PH, Kuhlenschmidt HL, Vancura BG, et al. Antimicrobial use in patients with advanced cancer receiving hospice care. *J Pain Symptom Manag* 2003; 25: 438–443.
37. Reinbolt RE, Shenk AM, White PH, et al. Symptomatic treatment of infections in patients with advanced cancer receiving hospice care. *J Pain Symptom Manag* 2005; 30: 175–182.
38. Thai V, Lau F, Wolch G, et al. Impact of infections on the survival of hospitalized advanced cancer patients. *J Pain Symptom Manag* 2012; 43: 549–557.
39. Ralston SH, Gallacher SJ, Patel U, et al. Cancer-associated hypercalcemia: morbidity and mortality. Clinical experience in 126 treated patients. *Ann Intern Med* 1990; 112: 499–504.