Malignancy-Related Hypercalcemia in Advanced Solid Tumors: Survival Outcomes

abstract

Purpose Malignancy-related hypercalcemia (MRH) is associated with a dismal prognosis. The widespread use of bisphosphonates (BPs), availability of more effective drugs in cancer treatment, and improvement in supportive care might have attenuated its impact.

Patients and Methods To assess overall survival (OS) of patients with MRH in a contemporary setting, we conducted a retrospective analysis of 306 patients with solid cancer hospitalized for symptomatic hypercalcemia. A multivariable Cox proportional hazards regression model was performed to evaluate possible prognostic factors associated with MRH.

Results All patients had serum ionized calcium > 5.5 mg/dL or total Ca > 10.5 mg/dL. Median age was 57 years, and the majority had squamous cell carcinoma (62%) and Eastern Cooperative Oncology Group performance status > 1 (96%). Head and neck was the most frequent primary site (28%). Forty-five percent had no previous chemotherapy (CT), and subsequent CT was administered to 32%. Eighty-three percent received BP with no survival gain. Median OS was 40 (95% CI, 33 to 47) days. Patients with a performance status > 2, altered mental status, C-reactive protein > 30 mg/L, albumin < 2.5 g/dL, or body mass index < 18 kg/m^2 had significantly poorer survival in a univariable analysis, and longer OS was related to treatment-naive patients, subsequent CT, and breast primary site. In the multivariable analysis, subsequent CT led to a median OS improvement of 144 versus 25 days (hazard ratio, 0.24; 95% CI, 0.14 to 0.40; *P* < .001).

Conclusion In a contemporary setting, MRH remains a marker of poor prognosis. Patients treated with CT had better survival, which suggests that appropriate treatment of selected patients might alter the course of this syndrome.

J Glob Oncol 3. © 2017 by American Society of Clinical Oncology Licensed under the Creative Commons Attribution 4.0 License

Ricardo Emanuel de Oliveira Ramos

Milena Perez Mak

Michel Fabiano Silva Alves

Gustavo Henrique Munhoz Piotto

Tiago Kenji Takahashi

Leonardo Gomes da Fonseca

Marina Cavalcanti Maroja Silvino

Paulo Marcelo Hoff

Gilberto de Castro Jr

Author affiliations and support information (if applicable) appear at the end of this article.

Corresponding author: Gilberto de Castro Jr, MD, PhD, Medical Oncology, Instituto do Cancer do Estado de São Paulo, Av Dr Arnaldo 251, 5th Floor, São Paulo, SP 01246-000, Brazil; e-mail: gilberto.castro@usp.br.

INTRODUCTION

In advanced cancers, hypercalcemia is a metabolic disorder that occurs in 10% to 30% of patients during the course of their disease[1] and leads to a 50% death rate within 30 days of diagnosis.[2] Since the 1990s, bisphosphonates (BPs) have been used in patients with bone metastasis to prevent or delay skeletal-related events; provide better symptom control[3]; and, thus, contribute to reduced hypercalcemia incidence.[4] BPs are effective in controlling hypercalcemia, with most patients achieving calcium control by day 10 (approximately 90% of those treated with zoledronic acid and approximately 70% with pamidronate).[5] However, the median time to relapse is short (range, 30-40 days with zoledronic acid and 17 days with pamidronate).[5] Retreatment of relapse and of primary refractory patients with a higher dose of zoledronic acid (8 mg) has proven less effective (response rate, 52%; median time to relapse, 8 days).[5]

Serum calcium normalization does not improve prognosis according to previous series, which prompts the need for antitumor therapy.[6] Besides the importance of BPs in the palliative care setting, some performance status (PS) amelioration is important until active cancer treatment can be started.

Given that few studies have evaluated the impact of cancer treatment in the outcome of patients with hypercalcemia,[2,7] whether the proper selection of patients and the use of newer therapies improve prognosis is not clear. We aimed to evaluate survival outcomes and prognostic factors in a contemporary series of patients with malignancy-related hypercalcemia (MRH).

PATIENTS AND METHODS

Three hundred six patients admitted from July 2009 to July 2012 to the oncology ward of Instituto do Cancer do Estado de São Paulo as a result of

Table 1. Patient Characteristics

Characteristic	No. (%)
Sex	
Male	200 (65)
Female	106 (35)
Median age, years (range)	57 (17-95)
Median time from diagnosis, days (range)	183 (0-4,114)
Histology	
SCC	190 (62)
Adenocarcinoma	68 (22)
Others	48 (16)
Primary site	
Head and neck SCC	85 (28)
Lung	47 (15)
Breast	32 (10)
Esophagus	31 (10)
Others	113 (36)
ECOG PS	
0	3 (1)
1	8 (3)
2	50 (17)
3	133 (45)
4	100 (34)
Bone metastasis	133 (43)
Altered mental status	168 (55)
No previous CT	137 (45)
Median laboratory parameters (range)	
Ionized Ca, mg/dL	6.6 (4.7-10.7)
Total Ca, mg/dL	12 (8.7-17.9)
Hemoglobin, g/dL	9.7 (3.9-15.4)
CRP, mg/L	129 (3-449)
Albumin, g/dL	2.9 (1.6-4.5)
CrCl, mL/min	60 (9.7-199)
BMI, kg/m^2	20 (11-49)
No. with hypercalcemia (range)	1 (1-5)
Hospice	69 (23)

Abbreviations: BMI, body mass index; CrCl, creatinine clearance; CRP, C-reactive protein; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; SCC, squamous cell carcinoma.

symptomatic hypercalcemia were included in this retrospective analysis. Eligible patients fulfilled the following criteria: biopsy-proven solid tumors and serum ionized calcium > 5.5 mg/dL (normal range, 4.6 to 5.3 mg/dL) or total Ca > 10.5 mg/dL (normal range, 8.6 to 10.2 mg/dL) within 3 days of admission. All patients had symptoms related to hypercalcemia, such as altered mental status,

dehydration, and constipation, or were referred by the treating physician for in-hospital management of hypercalcemia. Patients with concurrent causes of hospitalization also were included. Patients with chronic renal failure (glomerular filtration rate < 30 mL/min/1.73 m^2) before the episode of hypercalcemia and known primary hyperparathyroidism were excluded from this analysis. All data were extracted from medical records.

Overall survival (OS) was defined as the date of the first symptomatic hypercalcemic episode until death. Patients alive at the last date of contact were censored. Survival curves were estimated by the Kaplan-Meier method. To determine possible prognostic factors, log-rank test was used for univariable analysis. Variables with $P < .05$ were selected for the multivariable Cox proportional hazards regression model. This study was approved by the local ethics committee.

RESULTS

Patient Characteristics

Patient characteristics are listed in Table 1. Most were male (65%) with a median age of 57 years. Median time from diagnosis was 183 days. Squamous cell carcinoma was the most common histology (62%), and 68 patients (22%) had adenocarcinoma. Head and neck was the most frequent primary site (28%) followed by lung (15%), breast (10%), and esophagus (10%). The majority of patients (96%) had Eastern Cooperative Oncology Group PS > 1, with most having a poor PS (45% with PS 3 and 34% with PS 4). The incidence rate for bone metastasis was 43%, and 168 patients (55%) had altered mental status. Nearly one half had not received previous chemotherapy (CT) at presentation. Sixty-nine patients (23%) were transferred to hospice during hospitalization.

MRH Therapy

Two hundred forty-three patients (79%) were treated with pamidronate and 11 (4%) with zoledronic acid. Most (97%) were treated with intravenous fluid therapy, 238 (78%) with furosemide, 212 (69%) with calcitonin, and 172 (56%) with corticosteroids. Seventy-eight patients (25%) received only one line of CT, and 20 (7%) received two or more lines after the first hypercalcemic episode.

Prognostic and Survival Analysis

No difference in OS was seen between patients treated with BP or not (30 *v* 40 *v* 47 days for no BP *v* pamidronate *v* zoledronic acid, respectively;
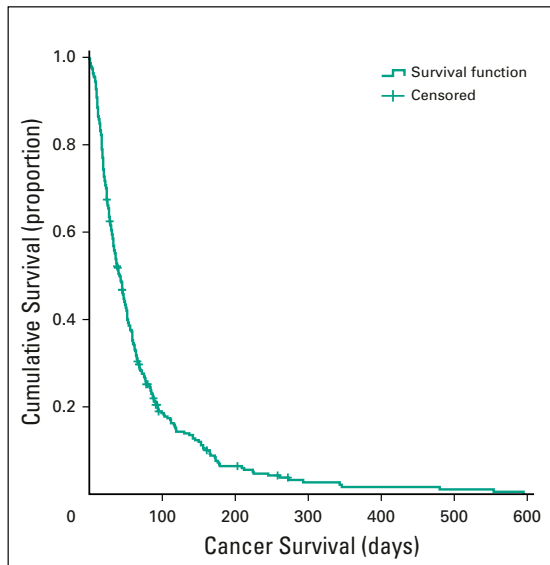
Fig 1. Median overall survival after hypercalcemia. Patients admitted with symptomatic hypercalcemia experienced a short overall survival of 40 days.

Fig 2. Chemotherapy (CT) survival impact in patients with symptomatic hypercalcemia. Patients who received additional CT had a significantly increased survival compared with patients who did not receive additional CT (144 *v* 25 days; *P* < .001).
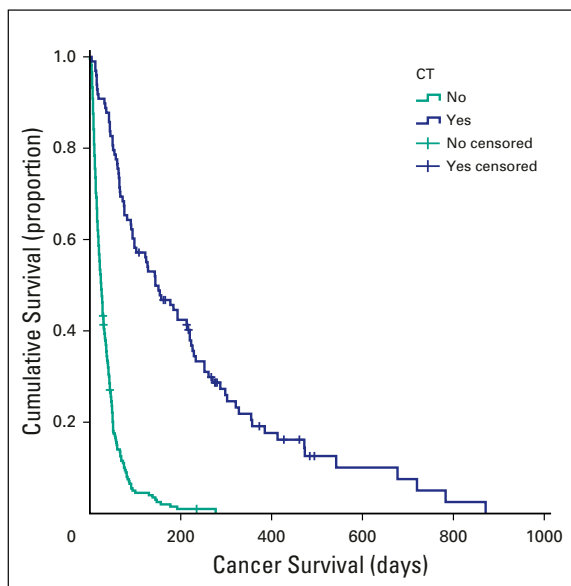
P = .73). Moreover, other supportive therapy, such as the use of corticosteroids, did not influence survival. Time from diagnosis also did not have an influence on survival (103 *v* 95 days, below and above the median time from diagnosis, respectively; *P* = .34).

Median OS (Fig 1) was 40 days (95% CI, 33 to 47 days). In the univariable analysis, PS > 1, altered mental status, C-reactive protein > 30 mg/L, albumin < 2.5 g/dL, and body mass index < 18 kg/m^2 were associated with a worse prognosis (Table 2). Longer OS was observed among patients who were treatment naive, treated with subsequent CT (144 *v* 25 days; *P* < .001), or had breast primary tumors (Table 2). In the multivariable analysis,

only subsequent CT remained a significant favorable prognostic factor for OS (hazard ratio, 0.24; 95% CI, 0.14 to 0.40; *P* < .001; Fig 2; Table 3).

DISCUSSION

In this single-center retrospective study, a median OS of 40 days was observed in patients with MRH treated with BPs, which is a similar result to that observed in other series published in the past 20 years[7-13] from various geographic regions. Studies of patients with breast cancer[8,14] showed a slightly better survival, which we also observed in the current series, that might be related to a greater exposure to systemic treatment and CT and/or hormonal sensitivity. In this large series of patients with symptomatic MRH, the most frequent primary site was head and neck in consonance with the European series of Penel and colleagues.[11,12] However, in another series by Soyfoo et al,[15] the breast was the most frequent site (29%) and showed head and neck as the fifth most common site (8%). Such differences could be attributed to regional characteristics and distinct inclusion criteria. To our knowledge, the current series is the largest to evaluate prognostic factors and survival in MRH. Penel et al[12] validated a prognostic score and showed that liver metastasis, squamous cell carcinoma, hypoalbuminemia, and total serum calcium levels > 11.3 mg/dL are related to a poor prognosis and that patients with at least one prognostic factor have a median OS of 49 days. In the current study, multivariable analysis showed that posthypercalcemia CT was related to survival gain: 144 days for patients who received one or more lines of CT versus 25 days for patients with no further CT. These findings are similar to those reported by Ralston et al[2] where the median OS was 135 days for patients who received CT after a hypercalcemic episode and 28 days for those with no further CT. Ling et al[7] also found a significant difference of 86 days for those with further cancer treatment and 35 days for those with no further treatment.

The limitations of the current study are related to its retrospective design. We excluded patients with known primary hyperparathyroidism but did not routinely measure parathyroid hormone levels in patients with hypercalcemia. Until recently, the real proportion of patients with hypercalcemia who had cancer of a benign nature was not clear. In a large series, Soyfoo et al[15] evaluated the etiology of hypercalcemia in patients with cancer and found that 199 (31%) of 642 patients had a non–cancer-related hypercalcemia cause. Among these patients, 115 had active disease and 84 were in

Table 2. Prognostic Factors: Univariable Analysis

Factor	Median OS, Days (Range)	P
ECOG PS		< .001
> 2	30 (24-36)	
0-2	98 (26-170)	
Altered mental status		< .001
Yes	24 (19-29)	
No	65 (50-80)	
CRP		.007
> 30 mg/L	36 (29-43)	
< 30 mg/L	94 (24-164)	
Albumin		.021
< 2.5 g/dL	20 (12-28)	
> 2.5 g/dL	41 (32-50)	
BMI		.025
< 18 kg/m^2	34 (23-45)	
> 18 kg/m^2	43 (35-51)	
Prehypercalcemia CT		.006
No	50 (38-62)	
Yes	31 (23-39)	
Posthypercalcemia CT		< .001
Yes	144 (87-201)	
No	25 (21-29)	
Primary site		.013
Breast	60 (3-117)	
Others	37 (30-44)	

Abbreviations: BMI, body mass index; CRP, C-reactive protein; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; OS, overall survival.

complete remission. By far, primary hyperparathyroidism was the leading cause (79%). In the current series, parathyroid hormone assessment was performed at the discretion of the treating physician, which is an inherent limitation of the restrospective nature of this report. Even so, four (10%) of 40 patients in whom such an issue was assessed had high levels of parathyroid hormone and were excluded from the final analysis. Such a difference can be explained by the fact that all the patients had active disease. Soyfoo et al also evaluated the etiology for MRH; bone metastases was the cause of 53% of the events, 35.3% were humoral in origin, and 11.7% were a result of both conditions.[15]

To improve these poor outcomes, some investigators have studied anti-RANKL (receptor activator of nuclear factor-κB ligand) therapies, such as denosumab and antiparathyroid hormone–related protein antibodies.[16] In a recent single-arm, phase II study, Hu et al[17] showed that denosumab is a promising treatment of MRH refractory to BPs, with a response observed in 21 of 33 patients and a median duration of 104 days.

Hypercalcemia seemed to be a marker of advanced and uncontrolled disease occurring mainly when more parathyroid hormone-related peptide or when extensive bone metastasis are present. Although BPs have led to faster calcium normalization, studies have failed to demonstrate survival gain (Table 4). Supportive therapy is essential for symptom control, which leads to improved quality of life[18] and high hospital discharge rates.[2] Given that most patients with MRH have a short survival time, a decrease of in-hospital stay is of particular interest for those in the final stages of life. Patients who receive home-based palliative care have significantly less symptom severity and distress, lower depression scores, and better physical health and quality of life than those who receive inpatient care.[23]

In this series, patients admitted to the hospital as a result of MRH had a median time from diagnosis of 6 months. The administration of CT after the first episode of MRH was related to a better survival, regardless of previous systemic treatment. This

Table 3. Prognostic Factors: Multivariable Analysis

Factor	HR (95% CI)	P
ECOG PS ⩾ 2	1.08 (0.62 to 1.89)	.79
Altered mental status	1.49 (0.97 to 2.29)	.068
CRP > 30 mg/L	1.22 (0.56 to 2.65)	.61
Albumin < 2.5 g/dL	1.29 (0.82 to 2.05)	.26
BMI < 18 kg/m^2	1.08 (0.73 to 1.58)	.72
No prehypercalcemia CT	0.93 (0.65 to 1.35)	.71
Posthypercalcemia CT	0.24 (0.14 to 0.40)	< .001
Breast primary site	0.99 (0.53 to 1.86)	.99

Abbreviations: BMI, body mass index; CRP, C-reactive protein; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio.

Table 4. OS, Histology, Primary Site, and BP Use in Large Series

First Author	No. of Patients	Main Histology (%)	Main Primary Site (%)	BP (%)	OS, Days
Warrell[19]	36	Adenocarcinoma (NS)	Breast (30)	No	29
Chasan[20]	27	RCC (100)	Kidney (100)	No	87
Ralston[2]	126	SCC (38)	Lung (45)	Yes (58)	30
Liaw[21]	28	SCC (100)	Head and neck (100)	No	42
Brada[14]	93	Adenocarcinoma (100)	Breast (100)	No	255
Fahn[22]	20	RCC (100)	Kidney (100)	NA	45
de Wit[8]	72	Adenocarcinoma (100)	Breast (100)	Yes (100)	135
Degardin[9]	173	SCC (100)	Head and neck (100)	NA	49
Ling[7]	114	NS	Breast (40)	Yes (100)	55
Penel[10]	136	SCC (85)	Head and neck (75)	Yes (36)	35
Penel[11]	260	SCC (44)	Head and neck (29)	Yes (100)	64
Penel[12]	252	SCC (42)	Head and neck (28)	Yes (100)	91
Le Tinier[13]	220	SCC (100)	Head and neck (66)	Yes (NS)	64
Ramos	306	SCC (62)	Head and neck (28)	Yes (83)	40

Abbreviations: BP, bisphosphonate; NA, not available; NS, not specified; OS, overall survival; RCC, renal cell carcinoma; SCC, squamous cell carcinoma.

suggests that MRH control could affect the disease course by allowing patients to receive cancer treatment and that the adequate selection of patients who should undergo CT could alter the course of this syndrome.

In conclusion, despite advances in oncologic treatment and supportive care, patients with symptomatic MRH still have a dismal prognosis, with little to no survival gain over the past decades. The role of new drugs, such as targeted therapies and denosumab, needs to be further elucidated in this context.

AUTHOR CONTRIBUTIONS

Conception and design: Ricardo Emanuel de Oliveira Ramos, Milena Perez Mak, Michel Fabiano Silva Alves, Gustavo Henrique Munhoz Piotto, Tiago Kenji Takahashi, Marina Cavalcanti Maroja Silvino, Paulo Marcelo Hoff, Gilberto de Castro Jr

Collection and assembly of data: Ricardo Emanuel de Oliveira Ramos, Michel Fabiano Silva Alves, Gustavo Henrique Munhoz Piotto, Leonardo Gomes da Fonseca, Marina Cavalcanti Maroja Silvino

Data analysis and interpretation: Ricardo Emanuel de Oliveira Ramos, Milena Perez Mak, Gustavo Henrique Munhoz Piotto, Tiago Kenji Takahashi, Marina Cavalcanti Maroja Silvino, Gilberto de Castro Jr

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

Ricardo Emanuel de Oliveira Ramos
No relationship to disclose

Milena Perez Mak
No relationship to disclose

Michel Fabiano Silva Alves
Travel, Accommodations, Expenses: Novartis, Bayer AG, Pfizer, Janssen-Cilag

Gustavo Henrique Munhoz Piotto
No relationship to disclose

Tiago Kenji Takahashi
Speakers' Bureau: MSD, Roche, AstraZeneca
Research Funding: Roche, Genentech (Inst), AstraZeneca, MSD

Leonardo Gomes da Fonseca
No relationship to disclose

Marina Cavalcanti Maroja Silvino
No relationship to disclose

Paulo Marcelo Hoff
Consulting or Advisory Role: AstraZeneca (I), Bayer AG (I)
Research Funding: Roche, Genentech

Gilberto de Castro Jr
No relationship to disclose

Affiliations

All authors: Instituto do Cancer do Estado de São Paulo, São Paulo, Brazil.

REFERENCES

1. Esbrit P: Hypercalcemia of malignancy—new insights into an old syndrome. Clin Lab 47:67-71, 2001

2. Ralston SH, Gallacher SJ, Patel U, et al: Cancer-associated hypercalcemia: Morbidity and mortality. Clinical experience in 126 treated patients. Ann Intern Med 112:499-504, 1990

3. Petrut B, Trinkaus M, Simmons C, et al: A primer of bone metastases management in breast cancer patients. Curr Oncol 15:S50-S57, 2008 (suppl 1)

4. Stewart AF: Clinical practice. Hypercalcemia associated with cancer. N Engl J Med 352:373-379, 2005

5. Major P, Lortholary A, Hon J, et al: Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: A pooled analysis of two randomized, controlled clinical trials. J Clin Oncol 19:558-567, 2001

6. LeGrand SB: Modern management of malignant hypercalcemia. Am J Hosp Palliat Care 28:515-517, 2011

7. Ling PJ, A'Hern RP, Hardy JR: Analysis of survival following treatment of tumour-induced hypercalcaemia with intravenous pamidronate (APD). Br J Cancer 72:206-209, 1995

8. de Wit S, Cleton FJ: Hypercalcemia in patients with breast cancer: A survival study. J Cancer Res Clin Oncol 120: 610-614, 1994

9. Degardin M, Nguyen M, Beaurin D, et al: Hypercalcemia and squamous cell carcinoma of the upper respiratory-digestive tracts. Incidence and prognosis [in French]. Bull Cancer 82:975-980, 1995

10. Penel N, Berthon C, Everard F, et al: Prognosis of hypercalcemia in aerodigestive tract cancers: Study of 136 recent cases. Oral Oncol 41:884-889, 2005

11. Penel N, Dewas S, Doutrelant P, et al: Cancer-associated hypercalcemia treated with intravenous diphosphonates: A survival and prognostic factor analysis. Support Care Cancer 16:387-392, 2008

12. Penel N, Dewas S, Hoffman A, et al: Cancer-associated hypercalcemia: Validation of a bedside prognostic score. Support Care Cancer 17:1133-1135, 2009

13. Le Tinier F, Vanhuyse M, Penel N, et al: Cancer-associated hypercalcaemia in squamous-cell malignancies: A survival and prognostic factor analysis. Int J Oral Maxillofac Surg 40:938-942, 2011

14. Brada M, Rowley M, Grant DJ, et al: Hypercalcaemia in patients with disseminated breast cancer. Acta Oncol 29: 577-580, 1990

15. Soyfoo MS, Brenner K, Paesmans M, et al: Non-malignant causes of hypercalcemia in cancer patients: A frequent and neglected occurrence. Support Care Cancer 21:1415-1419, 2013

16. Lumachi F, Brunello A, Roma A, et al: Cancer-induced hypercalcemia. Anticancer Res 29:1551-1555, 2009

17. Hu MI, Glezerman IG, Leboulleux S, et al: Denosumab for treatment of hypercalcemia of malignancy. J Clin Endocrinol Metab 99:3144-3152, 2014

18. Iwase M, Takemi T, Manabe M, et al: Hypercalcemic complication in patients with oral squamous cell carcinoma. Int J Oral Maxillofac Surg 32:174-180, 2003

19. Warrell RP Jr, Skelos A, Alcock NW, et al: Gallium nitrate for acute treatment of cancer-related hypercalcemia: Clinicopharmacological and dose response analysis. Cancer Res 46:4208-4212, 1986

20. Chasan SA, Pothel LR, Huben RP: Management and prognostic significance of hypercalcemia in renal cell carcinoma. Urology 33:167-170, 1989

21. Liaw CC, Huang JS, Wang JM, et al: Hypercalcemia in squamous cell carcinoma of the head and neck. J Formos Med Assoc 89:548-553, 1990

22. Fahn HJ, Lee YH, Chen MT, et al: The incidence and prognostic significance of humoral hypercalcemia in renal cell carcinoma. J Urol 145:248-250, 1991

23. Peters L, Sellick K: Quality of life of cancer patients receiving inpatient and home-based palliative care. J Adv Nurs 53: 524-533, 2006