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ORIGINAL ARTICLE

Cancer-associated hypercalcemia treated with intravenous diphosphonates: a survival and prognostic factor analysis

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Abstract
Background Cancer-associated hypercalcemia (CAH) is the most frequent metabolic disorder in cancer patients. We retrospectively reviewed the outcome and prognostic factors for patients with CAH being treated with standard intravenous disphosphonates.
Materials and methods Two hundred sixty patients were reviewed. Overall survival and prognostic factors were analyzed. Relative risks (RR) for early death (within 60 days) were assessed (Fischer exact test and logistic regression model).
Results Median survival was 64 days (range, 12–1,955+). Multivariate analysis identified the following factors as poor survival predictors: serum corrected calcium >2.83 mmol/l [hazard ratio (HR)=HR 2.21], albuminemia <35.5 (HR 2.41), squamous cell carcinoma (HR 2.64), bone metastasis (HR 1.44), and liver metastasis (HR 2..22). One hundred twenty-one patients died within 60 days. For those patients, the logistic regression model identified four independent predicting factors for early death: calcemia >2.83 mmol/l (RR 5.07), hypoalbuminemia (RR 7.42), liver metastasis (RR 4.34), and squamous cell carcinomas (RR 2.21).
Discussion Despite intravenous diphosphonate, CAH is still associated with poor outcome. Simple bedside parameters may estimate the risk of early deaths.

Keywords Cancer · Diphosphonates · Hypercalcemia · Supportive care · Prognosis

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Introduction

Hypercalcemia, defined as serum calcium superior to 2.60 mmol/l, is the most common metabolic disorder in patients with cancer [1–2]. Its incidence is estimated between 10 and 20% of all patients with cancer [1, 2]. Cancer-associated hypercalcemia (CAH) is either related to the paraneoplastic production of osteoclast-activating factor by cancer cells (humoral mediated hypercalcemia) or to the large direct osteoclastosis induced by cancer cells (local osteolytic hypercalcemia) [1].

The current management of CAH includes intravenous hydratation and infusion of diphosphonates [3–5]. Diphosphonates are effective inhibitors of osteoclastic activity and bind to calcified matrices, preventing the

attachment of osteoclastic precursors to the bone surface, being internalized selectively by bone-resorbing osteoclasts and consequently inhibiting osteoclast functions. Their molecular and cellular mechanisms of action are multiple, complex, and may include direct anti-tumoral based on apoptosis induction. [3–5].

The prognosis of CAH is very poor with a median survival ranging from 30 to 90 days for all primary sites, as reported in studies carried out before the widespread advent of diphosphonates [7, 8]. Despite its clinical efficacy, that is, normalization of serum calcium obtained in 40 to 100% patients with CAH [3–6], normalization of serum calcium observed within 4 days [3–6], and median duration of serum calcium normalization ranged between 11 to 48 days [3–6], the impact of pamidronate on overall survival is not clearly established [6, 9, 10].

The aim of this retrospective study was to characterize the factors that predict survival after a first episode of a CAH treated by intravenous disphosphonates. This study evaluates the prognostic value of variables easily obtained at patient bedside the day of diagnosis of CAH.

Materials and methods

Patients

Two hundred sixty consecutive patients treated at the Centre Oscar Lambret (Northern France Cancer Center) were reviewed. Inclusion criteria were (1) biopsy-proven solid tumors, (2) first episode of hypercalcemia, (3) hypercalcemia defined by serum albumin-corrected calcium above 2.60 mmol/l [11], and (4) treatment by intravenous diphosphonates. The calculation of albumin-corrected calcemia is based on the following rule: albumin-corrected calcemia=calcemia+[0.02×(40, albuminemia in g/l)].

For each case, we recorded age, sex of patient, primary site of disease, histology type, time between cancer diagnosis and first hypercalcemia episode, presence of visceral metastases in the most recent evaluation of cancer extension (bone, liver, lung, and brain), biological parameters (serum calcium, albumin, serum albumin-corrected calcium, and urea), need of hospitalization for treatment, and treatment with calcitonin.

This study was approved by the French "Commission Nationale Informatique et Libertés (CNIL, date of approval June 2005).

Statistical analyses

Population was described with median and extreme values for continuous variables and percentages with 95% confidence intervals for categorical variables.

Time to events was calculated from the day of the first hypercalcemia episode. The survival was assessed with the Kaplan–Meier method [12]. The influence of categorical variables on survival was investigated with the log-rank for univariate analysis [13] and then with a Cox proportional hazards model for multivariate analysis [14]. Only variables with p value<0.15 were selected for the multivariate analysis [14]. With those independent variables, we built a score aimed to predict early death, defined as death which occurred within the 60 days after the date of hypercalcemia episode.

Finally, we identified the variables that predicted early deaths by comparing patients' and disease's characteristics in patients with and without early death. The univariate analysis was based on the Fischer exact test and the multivariate analysis on a stepwise logistic regression model. In all cases, a p value inferior to 5% was considered as significant. Statistical analyses were carried out with SPSS, software, version 14.

Results

Patient data

There were 138 men and 122 women, aged from 2 to 91 years (median 56 years). Details of primaries and histolog-

Table 1 Primaries and histological subtypes

	Number of cases (%)
Primaries	
Head and neck	76 (29%)
Breast	52 (20.0%)
Esophagus	18 (6.9%)
Lung	17 (6.5%)
Uterine cervix	14 (5.3%)
Kidney	10 (3.8%)
Unknown primary	10 (3.8%)
Bladder	8 (3.0%)
Soft tissue	7 (2.7%)
Colon	4 (1.5%)
Prostate	4 (1.5%)
Brain	4 (1.5%)
Uterus	4 (1.5%)
Others	32 (12.3%)
Head and neck	76 (29%)
Histological subtypes	
Squamous cell carcinoma	114 (43.8%)
Adenocarcinoma	110 (43%)
Urothelial tumour	8 (3.0%)
Small cell cancer	3 (1.1%)
Liposarcoma	3 (1.1%)
Seminoma	2 (0.7%)
Others	18 (6.9%)

Table 2 Prognostic factor of overall survival (OS): univariate analysis with log-rank test

Variables[a]	Median OS in days (range)	*p* value
Hypercalcemia occurring within the first 4 months after cancer diagnosis	51 (234–67)	0.048
Other	77 (42–111)	
Male	45 (29–60)	0.028
Female	94 (5–182)	
Serum-corrected calcium>2.83 mmol/l	20 (13–26)	0.0001
Serum-corrected calcium≤2.83 mmol/l	254 (148–359)	
Albuminemia<35 g/l	19 (13–24)	0.0001
Albuminemia≥35 g/l	289 (153–424)	
Urea>7.1 mmol/l	34 (13–54)	0.0001
Urea≤7.1 mmol/l	147 (68–225)	
Head and neck cancers	45 (32–57)	0.005
Other primaries	98 (2–193)	
Squamous cell carcinomas	45 (32–57)	0.0001
Other histological subtypes	147 (40–253)	
Presence of bone metastasis	39 (18–59)	0.0001
Absence of bone metastasis	144 (46–241)	
Presence of liver metastasis	30 (15–44)	0.0001
Absence of liver metastasis	93 (31–154)	
Presence of lung metastasis	37 (16–57)	0.002
Absence of lung metastasis	77 (39–114)	
Presence of brain metastasis	11 (2–19)	0.001
Absence of brain metastasis	70 (43–96)	
In-patient treatment	34 (20–47)	0.0001
Out-patient treatment	377 (214–539)	
Treatment with calcitonin injections	17 (0–38)	0.004
Absence of treatment with calcitonin injections	74 (44–103)	

[a] Only variables found significant in univariate analysis are given herein (interval between date of cancer diagnosis and hypercalcemia, creatinin level, and alkaline phosphatases were not significantly associated with OS)

ical subtypes are shown Table 1. Metastases were seen in bone, liver, lung, and brain in 86 (33.0%), 66 (25.3%), 61 (23.4%), and 12 cases (4.6%), respectively. The median time interval between the diagnosis of cancer and occurrence of the first hypercalcemia episode was 3 months (range, 1–312). The median serum albumin-corrected calcium was 2.83 mmol/l (range, 2.61–4.56). Intravenous disphosphonates that have been used were pamidronate (n=230, 88.5%), clodronate (n=18, 6.9%), and zoledronate (n=12, 4.6%). Thirteen (5.0%) patients required calcitonin injections. Most of the patients (n=155, 59.6%) were inpatients.

Survival data

The median survival time of the entire cohort was 64 days (range, 12–1,955+). The following variables were found to be poor prognostic factors in univariate analysis: hypercalcemia occurring within the four first months after cancer diagnosis, male gender, serum albumin-corrected calcium over to 2.83 mmol/l, hypoalbuminemia, increased urea, head and neck cancers, squamous cell carcinomas, bone metastasis, liver metastasis, lung metastasis, brain metastasis, inpatients, and treatment with calcitonin injections (Table 2). In multivariate analysis, five independent variables remained significant: serum albumin-corrected calcium over to 2.83 mmol/l (p=0.007), hypoalbuminemia (p=0.001), squamous cell carcinomas (p=0.0001), bone metastasis (p=0.013), and liver metastasis (p=0.009) (Table 3).

One hundred twenty one patients (46.3%) died within the 60 days after the first hypercalcemia episode. In univariate analysis, the following variables were found predictive for early death: hypercalcemia episode present at the time of cancer diagnosis, male gender, hypoalbuminemia, urea superior to 7.1 mmol/l, albumin-corrected calcemia superior to 2.83 mmol/l, head and neck cancers, squamous cell carcinomas, bone metastasis, liver metasta-

Table 3 Prognostic factor of overall survival (OS): multivariate analysis with Cox model

Variables	Median OS in days (range)	p value	Adjusted hazard ratio (95% confidence interval)
Presence of bone metastasis	39 (18–59)	0.013	1.44 (1.09–2.11)
Absence of bone metastasis	144 (46–241)		Reference
Serum Corrected-calcium			
>2.83 mmol/l	20 (13–26)	0.001	2.21 (1.76–2.99)
≤2.83 mmol/l	254 (148–359)		Reference
Presence of liver metastasis	30 (15–44)	0.009	2.22 (1.76–2.89)
Absence of liver metastasis	93 (31–154)		Reference
Albuminemia			
<35 g/l	19 (13–24)	0.001	2.41 (1.87–3.32)
≥35 g/l	289 (153–424)		Reference
Squamous cell carcinomas	45 (32–57)	0.0001	2.64 (1.89–3.12)
Other histological subtypes	147 (40–253)		Reference

Table 4 Predicting factors for early deaths

Variables	Patients surviving < 60 days (early death; n=121)	Patients surviving > 60 days (n=139)	p value[a]	Adjusted odd ratio (95% CI)
Serum albumin-corrected calcium				
>2.83 mmol/l	94 (77.6%)	27 (19.4%)	0.001	5.07 [2.47–10.41]
≤2.83 mmol/l	27 (22.4%)	112 (80.6%)		Reference
Albuminemia				
<35 g/l	97 (80.1%)	24 (17.2%)	0.001	7.42 (3.65–15.06)
≥35 g/l	24 (19.9%)	115 (82.8%)		Reference
Squamous cell carcinomas	64 (52.8%)	41 (29.4%)	0.027	2.21 (1.09–4.48)
Other histological subtypes	57 (47.2%)	98 (70.6%)		Reference
Presence of liver metastasis	46 (38.0%)	20 (14.3%)	0.001	4.34 (1.86–10.10)
Absence of liver metastasis	77 (72.0%)	119 (85.7%)		Reference

[a] The multivariate analysis is based on a stepwise logistic regression model

sis, hospitalization required, and treatment with calcitonin injections. The final logistic regression model identified four independent predictive factors for early deaths: hypoalbuminemia, serum albumin-corrected-calcium over to 2.83 mmol/l presence of liver metastasis and squamous cell carcinomas (Table 4). Then, based on our multivariate analysis, we built a score aimed to predict early death (Table 5). The patients were classified according to four independent predicting factors: score=0 (absence of predicting factor), score=1 (presence of one predicting factors), and score=2 (presence of two or more predicting factor). Median survival time of patients with scores 1, 2, and 3 were 1,153, 213, and 19 days, respectively (p=0.001 with log-rank test; Fig. 1).

Discussion

Despite an adequate intravenous fluids hydratation and intravenous diphosphonate therapy, life expectancy of patients presenting a first episode of a CAH remains poor, with a median survival of 64 days in our series. This is in the range of what it has been published before the era of diphosphonates, when the median survival of CAH ranged from 30 to 90 days [2, 7, 8, 15–17]. There is no clear evidence that diphosphonate therapy improves outcome after CAH. Historical comparisons did no show any significant difference in survival between the survival curves of patients that have been treated with diphosphonates and those not have been treated with disphosphonates [10]. Surprisingly, overall survival was not reported in the largest randomized study, which has challenged the role of two diphosphonates [6]. Randomized comparisons of diphosphonates to placebo dealing with survival issues are lacking and will not be conducted due to their obvious unethical nature. Because alternative therapies such as gallium nitrate may be available [9], it could be worth to detect subgroups of patients who will not benefit from front-line diphosphonates. On the other hand, a modest and transient decrease in calcium level induced by diphosphonates may result in a clinical improvement of cognition disorders and, overall, a benefit in quality of life, which has to be taken into account in the medical decision making process.

The present multivariate analysis identified the following factors as predictors of poor survival: serum-corrected calcium >2.83 mmol/l, albuminemia <35 g/l, squamous cell cancer type, and presence of liver or bone metastases.

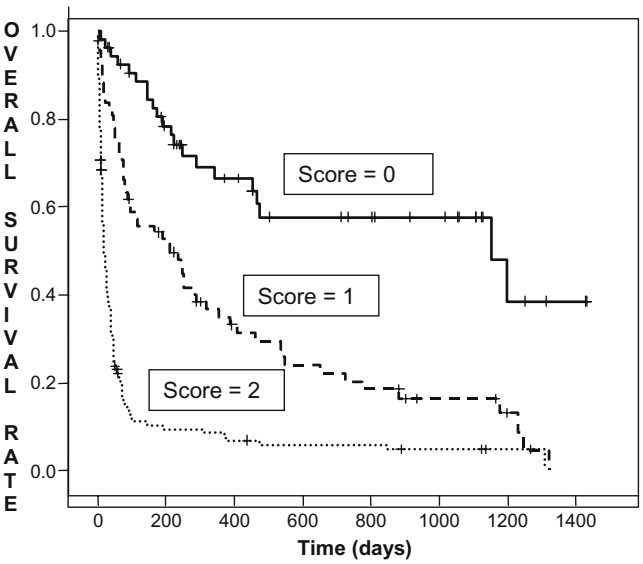

Fig. 1 Survival after first episode of hypercalcemia treated by diphosphonates according to selected prognostic factors. The patients were classified according to four independent predicting factors: serum-corrected calcium > 2.83 mmol/l, albuminemia < 35 g/l, squamous cell cancer type, and presence of liver or bone metastases. Score=0 (absence of predicting factor), score=1 (presence of 1 predicting factors), and score=2 (presence of two or more predicting factor)

Table 5 Survival after first hypercalcemia episode according to a predictive score

Score	Early death patients (n=121)	Patients surviving > 60 days (n=139)	Relative risk of early deaths (95% CI)	Median survival in days (range)
0 (n=40)	9	31	Reference	1,153 (350–1,955)
1 (n=35)	13	32	1.28 (0.62–2.68)	213 (69–356)
2 (n=175)	99	76	2.51 (1.39–4.53)	19 (12–25)

To our knowledge, our study is the largest one ever published on factors, which may predict survival of patients with CAH treated by intravenous disphosphonates (Table 6). The most potent predictive factor of shorter survival is the squamous cell nature of the primary. Patients with squamous cell tumors have a much shorter median survival (45 days) than patients with other histological subtypes (147 days). The particular poor prognostic of CAH associated with head and neck cancers has been consistently reported previously [9, 16, 18]. Actually, Cvitkovic et al. [9] have reported that pamidronate therapy was far less efficient in treating CAH episodes associated with squamous cell carcinomas than those associated with other histological subtypes. These findings may be explained by differences in terms of CAH mechanisms. In fact, CAH associated with squamous cell tumors of head and neck, esophagus, and lung is mainly related to abnormal parathyroid hormone related protein (PTHrp) tumor secretion [19, 20]. Moreover, there are several reports that suggest that diphosphonates, in general, and pamidronate, in particular, are less efficient when CAH is caused by PTHrp secretion [21–23]. The poor influence on survival of visceral metastases has been previously reported [2, 10, 24, 25], as well as high serum calcium levels [10, 25].

In our series, the absence of normalization of serum calcium has been confirmed as a poor prognostic factor, with a median survival of 26 days (2–31) for the 15 patients who did not respond to diphosphonate therapy. As this factor was not obtained at baseline but few days latter, we did not introduced it in our multivariate model.

To better select patients undergoing exclusive palliative care without chemotherapy in everyday practice, Auguston et al. [26] have recently introduced the concept of "early death." The key idea is to identify patients with very poor outcome, which may be considered for exclusive palliative care. Whereas Auguston et al. [26] focused their research on patients with multiple myeloma and found that older patients, those with increased level of beta2-microglobulin and those with poor performance status did have increased odds of early death, we found that hypoalbuminemia, serum albumin-corrected calcium superior to 2.83 mmol/l, liver metastasis, and squamous cell tumors were independent predictors of early death (Table 4). Moreover, we have built a simple bedside predictive model aimed to identify these patients with very poor outcome. As an example, the presence of two or more of the four predicting factors that have been selected after a stepwise regression procedure was able to predict a very short median survival (19 days; Fig. 1). For those patients, there is no doubt that palliative care must be considered.

The present study presents several limitations due to its retrospective nature. The mechanism of hypercalcemia was not explored and the non-cancer causes such as primary hyperparathyroidism were not systematically excluded. Our patients were not systematically considered for new evaluations of the cancer extension, especially new bone scan, which makes the presence or absence of bone metastases stated on the most recent evaluation.

Our study confirms the poor prognostic of patients with CAH, although they have been treated by adequate

Table 6 Prognostic factors and survival after hypercalcemia-related to cancer treated by diphosphonates

Study	Method	Number of cases	Median survival (months)	Prognostic factors (multivariate analysis)
De Wit and Cleton [24]	Retrospective	72	4.5	Duration of serum calcium normalization Visceral metastasis Level of alkaline phosphatases Primary treatment of cancer
Ling et al. [25]	Retrospective	114	1.8	Systemic available anticancer therapy Normalization of serum calcium
Truong et al. [27]	Retrospective	76	5	PTH-rp level (≥1 pmol/l)
Present study	Retrospective	260	2	Calcemia over 2.83 mmol/l Hypoalbuminemia (<35 g/l) Squamous cell carcinoma Bone and liver metastasis

disphosphonate therapy, and allows us to identify poor prognostic factors. Obviously, retrospective analyses are exploratory and serve to suggest testable hypotheses. In our case, the clinical use of the prognostic model we built depends on the results of an ongoing prospective validation with biological exploration of CAH mechanisms that we have launched.

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