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Cancer-associated hypercalcaemia in squamous-cell malignancies: a survival and prognostic factor analysis

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Abstract. The aim of this study is to analyse survival and prognostic factors in patients diagnosed with squamous cell carcinoma (SCC) presenting a first episode of cancer-associated hypercalcaemia (CAH). Retrospectively, the authors reviewed data from 220 patients with biopsy proven SCC who presented a first episode of CAH. They were treated in a single centre between 1995 and 2007. The survival analyses were done using the Kaplan–Meier method and Cox analysis. The primary endpoint was the overall survival from the date of hypercalcaemia episode. Median age was 55 years. Median survival was 64 days (1–197). Three independent prognostic factors were identified: brain metastasis (hazard ratio (HR) = 2.58 CI (1.03–6.45)), corrected calcaemia > 3 mmol/l (HR = 1.45 CI (1.05–2.01)) and hypoalbuminaemia (HR = 1.48 CI (1.07–2.04)). Using these factors, the authors performed a bedside prognostic score. In conclusion, median survival in patients diagnosed with SCC and CAH is extremely poor. The bedside prognostic score that the authors developed can help to anticipate patients' prognosis and adapt the treatment. This score needs to be validated on an independent cohort.

Key words: hypercalcaemia; squamous cell carcinoma; head and neck cancer; prognosis.

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Hypercalcaemia is the most frequent metabolic disorder seen in cancer patients[11]. The two main patho-physiological processes described for this disorder are: paraneoplastic syndrome with humoral factors released by the tumour in the absence of bone metastasis (i.e. parathyroid-hormone-related protein released); and osteoclast bone resorption locally induced by bone metastasis. Initial management of symptomatic cancer-associated hypercalcaemia (CAH) is mainly based on saline rehydration and bisphosphonates added to the specific cancer treatment[1,2,11]. Despite those treatments, which will most often correct the hypercalcaemia, patients with CAH have a poor prognosis, with a median overall survival ranging from 60 to 90 days[12]. In two previous studies, the authors developed and validated a reliable bedside prognostic score for CAH, whatever the primary and whatever the histology[13,14]. In the authors' series, the prognostic factors of adverse outcome were: serum albumin-corrected calcium > 2.83 mmol/l, hypoalbuminaemia, presence of liver metastasis and squamous cell carcinoma[12]. CAH is frequently diagnosed in different squamous cell primary sites whether or not associated with leucocytosis in the hypercalcaemia-leucocytosis syndrome [3–9,16,17].

Squamous cell carcinoma (SCC) appeared as an independent prognostic

factor in the authors' previous analysis, so in this study they focus more specifically on the survival and prognostic factors of cancer patients diagnosed with SCC who present with a first CAH episode. The aim was to refine and customize the prognostic model to patients with SCC and patients with SCC arising in the head and neck. This subpopulation of vulnerable patients usually displays many adverse prognostic factors and severe underlying social and medical conditions; so it is necessary to tailor the previously described predictive factors to this subpopulation.

Materials and methods

The authors reviewed the data of 220 consecutive patients treated at the Centre Oscar Lambret from January 1995 to June 2007. The inclusion criteria were: biopsy proven SCC, first episode of CAH and hypercalcaemia defined by serum albumin-adjusted calcium above 2.60 mmol/l. For each case, the authors recorded age, sex of patient, primary site of disease (head and neck, lung cervix and oesophageal cancers), time between cancer diagnosis and this first hypercalcaemia episode, presence of visceral metastases (liver, lung, bone and cerebral) and biological parameters (albumin, serum albumin-corrected calcium, urea, serum creatinine, haemoglobin level and lymphocyte and neutrophil count, C-reactive protein level, serum alkaline phosphatase and lactate dehydrogenase (LDH)).

The primary endpoint was the overall survival from the date of hypercalcaemia episode (estimation by Kaplan–Meier method).

Statistical analysis

Univariate Cox model analysis was used to identify prognostic factors amongst continuous variables. According to observed median values, the authors dichotomized the continuous variables associated with prognostic significance ($p < 0.05$) in univariate analysis. Nevertheless, the optimal cut-off of corrected hypercalcaemia that maximizes its prognostic value was identified by area under the receiver operator curve (AU-ROC). The authors had used log-rank tests to identify prognostic parameters amongst categorical variables. All parameters associated with significance ($p < 0.05$) had been introduced in a multivariate model (Cox analysis).

Results

There were 220 patients with a histologically proven SCC (161 male; 59 female). Their characteristics are described in Tables 1 and 2. Their median age was 55 years (range 33–86 years). The head and neck is the main primary site represented (129/220). Node involvement and distant metastasis were present in 58% and 28% cases, respectively. The most frequent metastatic sites were lung (29%) and bones (28%). Concerning the biological parameters, 79 patients (36%) had

Table 1. Continuous variables: median, range and prognostic value in univariate analysis.

Variables (unit)	Normal range	Median	Range	P^*
Age (years)	–	55	33–86	0.327
Corrected calcium (mmol/l)	2.2–2.6	2.87	2.61–5.42	0.0001 (↑)
Serum creatinine (μmol/l)	44–80	76	26–460	0.625
Serum urea (g/l)	<8.3	7	2–41	0.176
Serum albumin (g/l)	40–49	32	19–51	**0.0001** (↑)
Neutrophil count (/mm^3)	1,500–7,000	11,108	2,851–32,689	0.065
Lymphocytes count (/mm^3)	1,500–4,000	1,014	164–4,214	**0.014** (↓)
Haemoglobin (g/l)	12–16	11.7	7–16	**0.001** (↓)
C-reactive protein (mg/l)	<6	82	0–389	0.500
Alkaline phosphatase (UI/l)	35–105	103	35–740	0.951
LDH (UI/l)	240–480	330	189–9,120	0.768

* Prognostic value as continuous variable estimated by Cox univariate analysis; arrows show the direction of the prognostic effect.

Table 2. Categorical variables as prognostic factors of overall survival.

Categories	*n*	Median OS (days)	*p*
All	220	64	–
Men	161	53	
Women	59	118	0.580
Lung cancer	9	49	0.115
Cervix	7	53	0.230
Unknown primary	7	56	0.257
Head neck (NS)	73	55	0.320
Hypopharynx	14	78	0.134
Larynx	9	72	0.433
Oesophagus	27	45	0.114
Oropharynx	52	57	0.163
Vulva	6	70	0.439
Others	5	71	0.351
T4	37	58	
T1–T3	183	83	0.517
N+	128	49	
N−	84	76	0.113
Bone met. (+)	62	45	
Bone met. (−)	158	70	0.028
Liver met. (+)	47	32	
Liver met. (−)	173	89	0.092
Lung met. (+)	65	54	
Lung met. (−)	155	70	0.450
Brain met. (+)	5	2	
Brain met (−)	215	70	**0.026**
Serum corrected calcium ≥ 3 mmol/l	79	20	
Serum corrected calcium < 3 mmol/l	141	99	**0.0001**
Albumin < 32 g/l	105	31	
Albumin ≥ 32 g/l	115	123	**0.0001**
Neutrophil > 10,000/mm^3	110	44	
Neutrophil ≤ 10,000/mm^3	109	99	0.053
Lymphocytes > 1000/mm^3	109	51	
Lymphocytes ≤ 1000/mm^3	110	99	**0.036**
Haemoglobin ≤ 11 g/l	69	14	
Haemoglobin > 11 g/l	148	113	**0.019**

NS: Not specified or multiple head and neck cancers.