in vivo *28*: 863-866 (2014)

Use of Surgery and Carboplatin in Feline Malignant Mammary Gland Neoplasms with Advanced Clinical Staging

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Abstract. *Background/Aim: Feline mammary carcinomas (FMCs) are characterized by poor prognosis and little progress has been made in extending patient survival. The aim of the study was to compare overall survival periods of FMCs submitted to different treatment protocols, including surgery and adjuvant chemotherapy. Materials and Methods: Analysis of conventional surgical excision alone or in association with adjuvant chemotherapy with carboplatin in sixteen cats diagnosed with stage III and grade II or III FMCs was performed. Results: Patients treated with surgery and chemotherapy presented a longer overall survival (OS) than those treated only with surgery, however, no statistical difference was observed when comparing both treatments (p=0.883). Conclusion: Therapeutic benefit of carboplatin remains invalidated for FMCs and further investigation regarding adjuvant therapies are warranted. Surgery remains as the gold treatment in FMCs.*

Feline mammary neoplasms are the third most frequent tumors, following hematopoietic and cutaneous neoplasms (1-4). The average age of diagnosis is 10 to 11 years (2) and neutered animals are less likely to develop tumors than intact cats (4). In contrast to humans and canines, at least 80% of all feline mammary tumors are malignant (5, 6). Furthermore, ulceration and lymphatic vessel invasion are common, and regional or distant metastasis may be observed in over 80% of felines with malignant mammary neoplasms (4).

Surgery remains the treatment of choice for feline mammary neoplasms (2) and may be used alone or in combination with chemotherapy or other modes of cancer therapy when malignant (4). Chain mastectomy is the surgical method of choice, regardless of the size of the tumor, due to a reduction of local tumor recurrence. However, no increase in overall survival (OS) time was observed (1, 4, 7). One previous study found a significant difference in OS associated to surgical procedures; cats that received bilateral radical mastectomies had the longest survival times (8). Early detection and aggressive treatment are notably important for feline mammary carcinomas (FMCs) (9). The response to chemotherapy may be poor once metastasis has occurred (10).

Available chemotherapy protocols for feline mammary neoplasms consist of doxorubicin as a single agent or in combination with cyclophosphamide, carboplatin as a single agent or in combination with doxorubicin and the association of mitoxantrone with cyclophosphamide (4, 11, 12). Additional clinical trials are required to assess which chemotherapeutic doses and combinations are the most effective in increasing survival time (10).

A previous study associated longer OS times for FMCs treated with surgery and adjuvant doxorubicin chemotherapy, although no control population was included (8). Another study found similar median OS time when treating FMCs with surgery, doxorubicin, and Cox-2 inhibitors; however it also lacked a control population (13). No overall benefit to such adjuvant chemotherapy was observed in a different study that compared surgery-plus-chemotherapy to surgical treatment-alone (7). In addition, doxorubicin can be nephrotoxic in cats and careful evaluation of renal function is recommended (4).

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Key Words: Feline, mammary gland, neoplasm, chemotherapy, carboplatin.

Little progress has been made in extending the survival time of patients with feline mammary tumors, characterized by a guarded to poor prognosis and median OS of less than one year (3, 4). Therefore, the aim of this study was to compare OS periods of FMCs submitted to different treatment protocols, including surgery and adjuvant chemotherapy with carboplatin.

Materials and Methods

Animals and staging. A retrospective analysis of sixteen cats admitted at the Veterinary Teaching Hospital of the Federal University of Minas Gerais, Brazil, was performed. The animals were divided into two groups according to two different treatments protocols: 9 animals presenting FMCs submitted solely to unilateral radical mastectomy as the surgical treatment and 7 animals presenting FMCs submitted to conventional surgical excision and medication with four intravenous cycles of carboplatin at a dose of 200 mg/m^2, with a 21-day interval. Animals were treated solely with surgery mainly due to refusal of chemotherapy treatment by the pet owner.

Cases were staged according to a modified World Health Organization clinical staging system for feline mammary tumors. This system evaluates the tumor size (T_1: 0-2 cm; T_2: 2-3 cm; T_3: >3 cm), the neoplastic involvement of regional lymph nodes (N_0: no metastasis; N_1: metastasis) and the presence of distant metastasis (M_0: no metastasis; M_1: metastasis). Afterwards, cases are divided into four stages: I ($T_1N_0M_0$), II ($T_2N_0M_0$), III ($T_3N_{0-1}M_0$, $T_{1-2}N_1M_0$) and IV ($T_{1,2,3}N_{0-1}M_1$) (7, 13).

Tissue processing and evaluation. Tumor specimens were collected, fixed for 48 h in 10% neutral buffered formalin solution and embedded in paraffin. Subsequently, 4-μm histological sections were obtained and stained with hematoxylin and eosin (H&E). Tumors were classified according to veterinary histological criteria (6).

Histological grade of the tumors was established according to the Nottingham system (14). This system evaluates tubule formation index (1 point: more than 75% of the tumor is composed by tubules, 2 points: between 10% and 75% of tubular formations and 3 points: tubules occupy 10% or less of the tumor), nuclear pleomorphism (1 point: small and regular nuclei, 2 points: moderate increase in size and variation of nuclei, 3 points: marked pleomorphism with large variation in size and shape of nuclei) and mitotic count (1 point: 0-8 mitoses, 2 points: 9-16 mitoses and 3 points: above 17 mitoses in 40× lens). Histological grade of the tumor is obtained through the sum of the scores which results in a total amount that ranges from 3 to 9. Afterwards, the tumor is classified as grade I (3-5 points), grade II (6-7 points) and grade III (8-9 points).

Patient follow-up was obtained through the evaluation of patient medical records and telephone interviews to owners in order to evaluate disease evolution with possible recurrences and metastases. In order to select more uniform cases, queens were excluded from the analysis when tumors were initially diagnosed as grade I, or classified as stage I, II, or IV.

OS time was defined as the period (in days) between the date of surgical removal of the tumor and death caused by the disease. Animals that died from unknown causes or causes unrelated to the tumor were censored.

Statistics. OS was evaluated by univariated analysis (Kaplan-Meier estimated survival curves). Values were considered statistically significant when $p<0.05$ by the log-rank test (Cox-Mantel). Median survival was defined as the period when 50% of patients of a determined group died.

All procedures were performed under the appropriate guidelines and with the approval of the Ethics Committee for Animal Experimentation (CETEA/UFMG), protocol 13412/2012.

Results

The 16 FMCs evaluated were histologically diagnosed as: seven (43.75%) cribriform carcinomas, four (25.00%) tubulopapillary carcinomas, one (6.25%) papillary carcinoma, one (6.25%) micropapillary carcinoma, one (6.25%) solid carcinoma, one (6.25%) tubular carcinoma and one (6.25%) glycogen rich clear cell carcinoma.

Regarding histological grade, 16 invasive carcinomas were evaluated as: ten (62.50%) grade II and six (37.50%) grade III. All (100.00%) patients evaluated for clinical staging were classified as stage III.

Carboplatin administration was well-tolerated by patients. Minimal side-effects were observed, such as myelossupression at the drug's nadir period and occasional and discreet gastrointestinal complications.

Median patient follow-up time was 202 days (ranging from 1 to 1,400 days). Among patients submitted only to the surgical treatment, four (44.45%) died due to the progression of the FMC, three (33.33%) died due to other reasons and two (22.22%) remained alive at the end of follow-up. Among patients submitted to conventional surgical excision and adjuvant chemotherapy with carboplatin, five (71.44%) died due to the progression of the FMC, one (14.28%) died due to other reasons and one (14.28%) remained alive at the end of follow-up.

Patients treated only with surgery presented a median survival of 387 days, while those treated with surgery and chemotherapy presented a median survival of 428 days. No statistical difference was observed when comparing the OS of the two different treatment groups, with $p=0.883$ (Figure 1).

Discussion

Tubular, papillary, solid and cribriform carcinomas are described as the most frequent invasive histological types found in the feline mammary gland, and some carcinomas show a combination of histological types in one neoplasm (4, 10). Although the studied patients presented diversified malignant histological types, a poor prognosis was seen in all cases due to moderate or poor differentiation and advanced clinical staging. To the authors' knowledge, this is the first study that attempts to include a more uniform population in control and treated with adjuvant chemotherapy groups. In addition, previous studies failed to

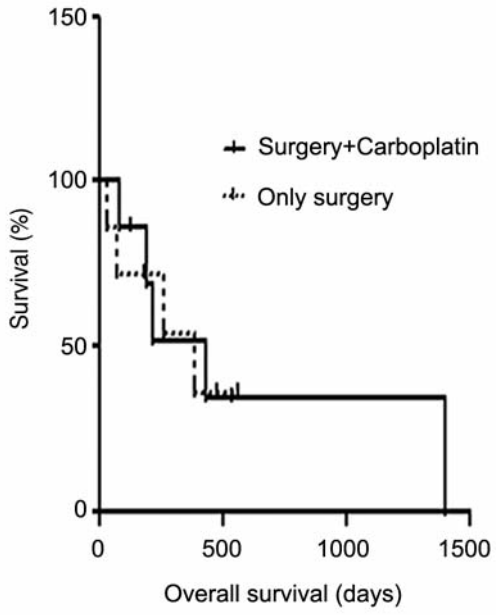

Figure 1. *Overall survival curves for 16 female cats according to therapy. Patients submitted to surgical treatment alone, 9 cases (-----); and conventional surgical excision and carboplatin, 7 cases (– –) (p=0.883).*

maintain a standard protocol for chemotherapy (including dosage, association of other drugs and number of cycles) (7, 8, 13); in the present study queens included in each group received identical treatments.

The Elston and Ellis method is the most common method for histological grading of invasive carcinomas and is strongly correlated to prognosis (15). FMCs are mainly classified as moderately-or poorly-differentiated (10, 15, 16), as was found in this study.

In the present study, all cases were clinically staged as stage III, characterized by tumors larger than 3 cm and/or regional lymph node metastasis. Feline mammary tumors larger than 3 cm are associated with a poor prognosis by several authors (1, 4, 9, 12, 13, 17). Lymphovascular invasion and lymph node metastases are significantly associated with lower survival rates and are considered independent prognostic predictors (15).

Carboplatin is indicated for the treatment of canine and feline malignant mammary gland neoplasms (11). Adjuvant chemotherapy with carboplatin has been proven to be beneficial in the treatment of dogs with canine mammary tumors with advanced clinical staging (18). The drug was also used as a rescue therapy agent alone or in association to other chemotherapy drugs (mitoxantrone and doxorubicin) for FMCs presenting recurrences or metastases (8). In this study, although the patients treated with adjuvant chemotherapy presented longer median OS, no significant statistical difference was observed when comparing the OS of feline patients treated only with surgery or surgery associated to carboplatin. This could be due to some limitations of the design of the study, characterized by a retrospective and nonrandomized analysis with a small number of animals. The OS for both treatment groups were higher than that described in the literature (3, 4), demonstrating the efficacy of the chosen surgical treatment, which remains the gold standard treatment in FMCs.

Acknowledgements

Supported in part by the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP), Fundação de Amparo a Pesquisa de Minas Gerais (FAPEMIG), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES).

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Received May 21, 2014
Revised July 7, 2014
Accepted July 8, 2014