Evaluation of metronomic chemotherapy using low dose cyclophosphamide in dogs with solid tumors

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Introduction

Metronomic chemotherapy with low dose cyclophosphamide (MCTX) has been used increasingly within veterinary patients following the results of studies demonstrating efficacy in dogs with splenic haemangiosarcoma[1], incompletely resected soft tissue sarcomas[2-3] and osteosarcoma[4] with minimal toxicity (haematological, gastrointestinal, renal, urinary). No study has yet assessed the use of cyclophosphamide-based metronomic chemotherapy in a large patient population with varying tumour types.

Aims

1. Identify the prevalence of toxicity (haematological, gastrointestinal, renal, urinary) in patients treated with MCTX.
2. Assess the outcome of dogs with different tumour types and disease stage treated with MCTX.

Hypotheses

-Toxicity to MCTX would be low in dogs with solid neoplasia, regardless of cyclophosphamide regime.
-MCTX would provide prolonged progression free intervals and survival times in dogs with microscopic disease compared to those with macroscopic disease.

Materials & Methods

Medical records were screened retrospectively for canine patients receiving MCTX over 4 years for a minimum of four weeks therapy and with follow-up information available. Signalment, tumor type, stage, MCTX dose, regimen, concurrent medications/therapies, adverse effects and response were recorded. If required, data was collected from referring veterinarians. Toxicity was graded as per the criteria in the VCOG-CTCAE version 1.1[5].

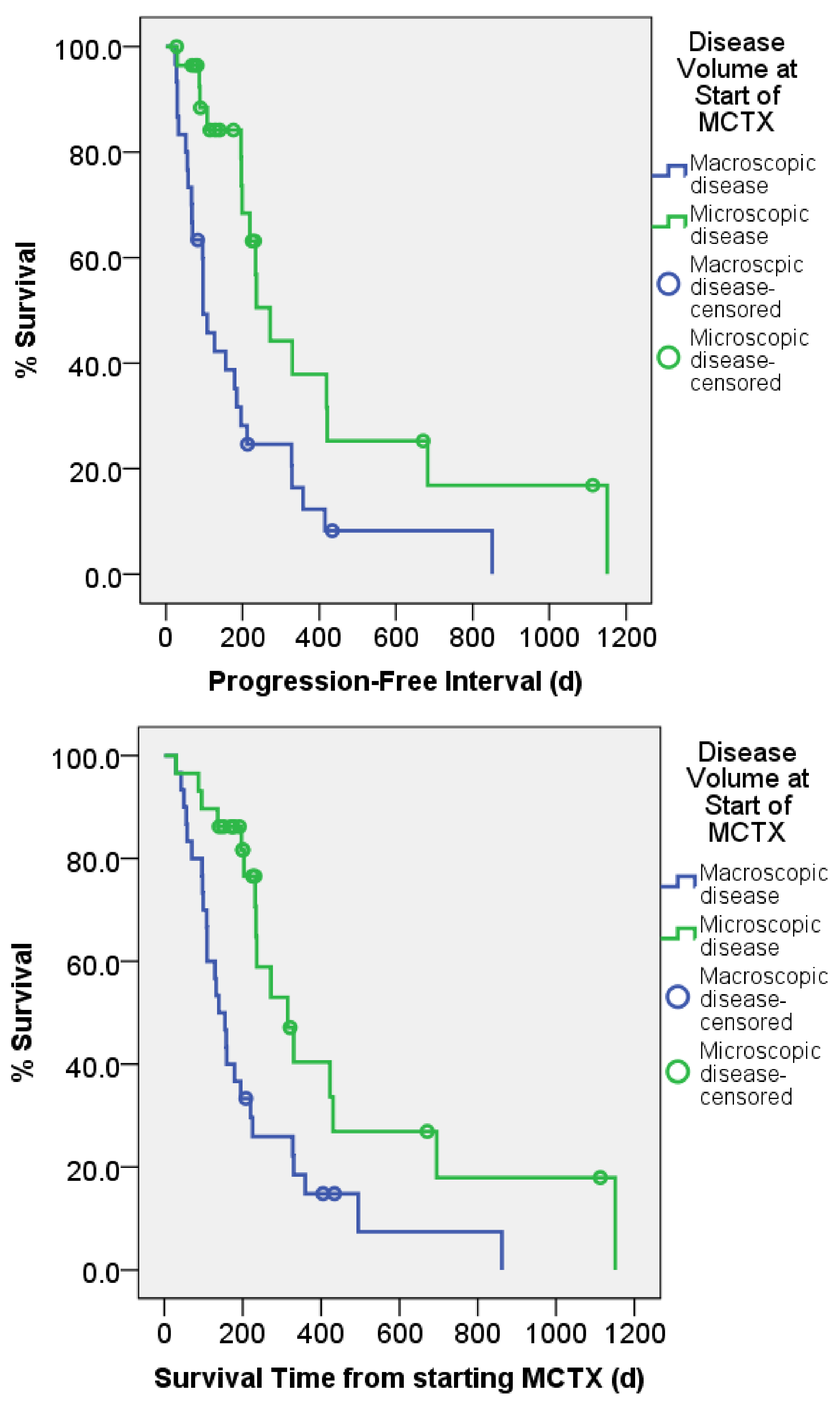

Figure 2: Progression-free interval (PFI) and survival time from starting MCTX (ST) in canine patients treated with MCTX since 2009, stratified by disease volume at the start of MCTX. The median PFI of 272 days and the median ST of 315 days in dogs with microscopic disease at the start of MCTX was statistically different (*P* value 0.002 for PFI and *P* value 0.003 for ST by log-rank analysis) from the 97 day median PFI and 139 day median ST of dogs with macroscopic disease at the start of MCTX.

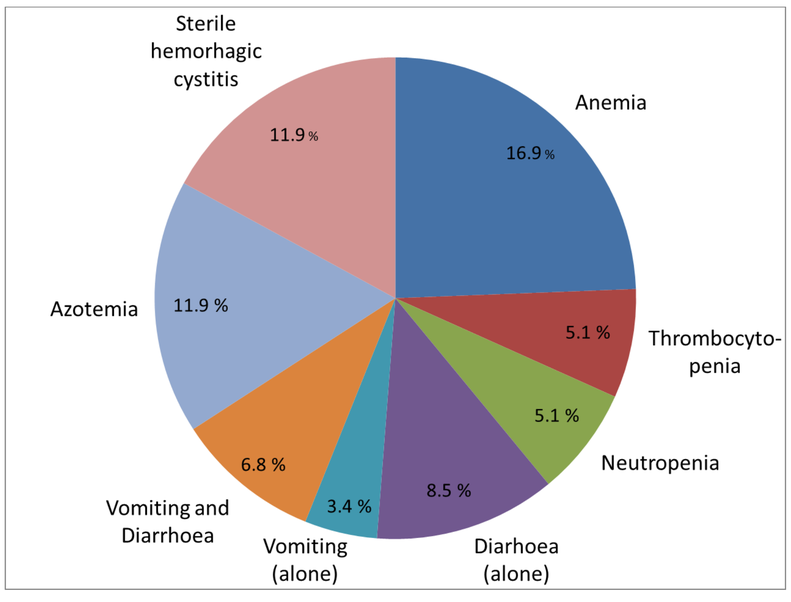

Figure 1: Toxicity (hematological, gastrointestinal, renal and urinary) developed in canine patients treated with MCTX. Grade 1-2 anemia (16.7%) and azotemia (11.9%) were the most commonly noted adverse effect, with sterile hemorrhagic cystitis also noted in 11.9% of patients.

Conclusions

MCTX was well tolerated overall, with minimal severe toxicity. Potential improved control in microscopic disease management has been suggested, but further studies are warranted to fully justify the best setting for its use.

Results

59 canine patients were eligible for inclusion (30 with carcinomas, 22 with sarcomas and 7 with other tumor types). 30 patients were identified with macroscopic disease whilst 29 were identified with microscopic disease. The most common regimen of cyclophosphamide administration was every other day (n=39) at a mean dose rate of 11.7mg/m^2 (range 6.6-16.6 mg/m^2). Meloxicam was the most frequently used NSAID (n=38) at 0.2mg/kg once daily. Median MCTX treatment length was 227.9 days (range 27-1151d). Toxicity was noted in 57% of patients with grade 1-2 anemia and azotemia being the most common. Grade 3 sterile hemorrhagic cystitis was noted in 11.9% of dogs with a median development time of 225 days (range 77-665d). 53% of dogs developing toxicity were treated with 10mg/m^2 cyclophosphamide every other day. 12/30 dogs with macroscopic disease and 8/29 dogs with microscopic disease had stable disease. Median progression-free interval (mPFI) and median survival time from starting MCTX (mST) was longer in patients with microscopic disease (PFI 272 days, ST 315 days; range 30-1151d) compared to those with macroscopic disease (PFI 97 days, range 30-851d; ST 139 days, range 30-862d). No difference in mPFI or mST was noted between patients with carcinomas (PFI 196 days, range 25-1113d; ST 235 days, range 30-1113d) compared to those with sarcomas (PFI 199 days, range 28-1151d; ST 232 days, range 30-1151d).

Acknowledgments

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