Quality of life assessment in cancer patients receiving single-agent versus multidrug chemotherapy protocols

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Abstract

Background: Quality of life (QoL) is an essential factor in therapeutic decision-making for human patients and is commonly used as an endpoint in clinical trials of cancer treatments.

Aim: To compare owners’ perception of QoL in canine and feline patients affected by different tumor histotypes treated with single-agent or multidrug protocols.

Methods: Owners were asked to assess the impact on QoL of their pets undergoing chemotherapy treatment by answering a questionnaire and assigning a score to different health-related parameters reported to affect QoL.

Results: Questionnaires of 101 patients (85 dogs and 16 cats), collected at different time points, were analyzed. Fifty-seven patients were given single-agent chemotherapy (carboplatin, doxorubicin, lomustine, melphalan, mitoxantrone, vinblastine, and vinorelbine), whereas 44 were given multiple-agent treatment. When diverse factors including chemotherapy treatment type (single-agent vs. multidrug regimens) and the onset and kind of adverse effects were considered, no significant variations in owners’ perceptions of their pets’ QoL were discovered.

Conclusion: Chemotherapy type (single-agent vs. multidrug protocol) and related adverse events are shown, which did not influence owners’ perception of their pet’s QoL. Future prospective studies should look into clinical characteristics that might affect QoL, such as the patient’s age, tumor stage, and protocol purpose (curative vs. palliative).

Keywords: Canine, Chemotherapy, Feline, Quality of life, Tumor.

Introduction

Quality of life (QoL) as a measurable parameter is a relatively recent concept, which has gained increasing importance in veterinary medicine over the last decade (Yeates and Main, 2009). There is no universally accepted definition of QoL, but it is generally considered a multidimensional concept that involves subjective evaluation of factors that contribute to the overall well-being (Osaba, 2011; Giuffrida and Kerrigan, 2014; Yousefi et al., 2016). One of the fundamental goals in managing cancer patients, especially in a palliative setting, is to maintain the best possible QoL, independently of the tumor type affecting the patients and despite any implemented treatment (Hamilton et al., 2012).

As perceived by owners, poor QoL has been reported as a common reason for euthanasia (Edney, 1998), and therapeutic success is also defined based on owners’ perception of their pets’ QoL (Levine et al., 2008). In veterinary oncology, several studies have focused on the impact of a particular type of chemotherapy protocol on owners’ perception of their pets’ QoL. Bowles et al. (2010) showed that the majority of owners positively described the experience of their animals undergoing carboplatin-based chemotherapy.

Two studies have so far evaluated owners’ perception of QoL in dogs and cats affected by lymphoma (LSA) and receiving multidrug protocols; in both cases, owners reported that the treatment did not negatively impact the QoL of their pet (Mellanby et al., 2003; Tzannes et al., 2008). When deciding on a course of antineoplastic treatment, most owners consider several factors, including prognosis, time commitment, costs, and potential occurrence of adverse events (AEs). When compared to single-agent protocols in human medicine, multidrug protocols may increase response rates and even prolong progression-free survival, despite being associated with an increased rate of treatment-associated AEs (Kumar and Chakraborty, 2016). However, two early studies showed that increased toxicity does not always negatively impact QoL (Funaioli et al., 2008; Huober and Thurlimann, 2009).

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In most cases, when exploring the impact of AEs on QoL in human medicine, not only gastrointestinal and hematological toxicity are evaluated, but also more specific chemotherapy-related AEs (such as hand–foot syndrome and peripheral neuropathy) and cosmetic side effects (such as alopecia), potentially affecting the patient’s perception of QoL (Funaioli et al., 2008). Single-agent protocols in veterinary medicine have historically and anecdotally been associated with fewer side effects than multidrug protocols, and thus may be offered by clinicians as a first-line treatment option in elderly patients or in cases where owners do not accept the risk of their pet experiencing severe AEs (Moore and Frimberger, 2018). In a previous study evaluating factors potentially influencing owners to treat their pet with chemotherapy, vomiting was considered an acceptable side effect, but inappetence, weight loss, and depression were deemed to be unacceptable (Williams et al., 2017).

At present, no studies are assessing any differences in QoL, as perceived by pet owners, in dogs and cats receiving single-agent versus multidrug protocols, and there are no results to guide clinicians when discussing treatment options for pets with cancer.

The authors’ primary goal was to assess owners’ perceptions of their pets’ QoL while they were receiving single-agent versus multidrug protocols, and thus may be offered by clinicians as a first-line treatment option in elderly patients or in cases where owners do not accept the risk of their pet experiencing severe AEs (Moore and Frimberger, 2018). In a previous study evaluating factors potentially influencing owners to treat their pet with chemotherapy, vomiting was considered an acceptable side effect, but inappetence, weight loss, and depression were deemed to be unacceptable (Williams et al., 2017).

Materials and Methods

A modified, translated version of a previously published questionnaire (Lynch et al., 2010) (Table 1) was given to owners of dogs and cats with newly diagnosed different tumor types, receiving MTD chemotherapy as part of a single-agent or multidrug protocol. Questionnaires were collected from four different European institutions from 2018 until 2019. Owners were asked to fill the questionnaire at different time points during the chemotherapy course, specifically prior to treatment start, while receiving chemotherapy, and at the end of the protocol. All the drugs used were administered at their published MTD; single-agent chemotherapy was defined as a protocol including one cytotoxic drug, whereas multidrug protocols included different chemotherapy agents. Single-agent protocols included carboplatin (Rassnick et al., 2001; Kisseberth et al., 2008), chlorambucil (Vail et al., 2020), doxorubicin (Gustafson and Bailey, 2020), gemcitabine (Elpiner et al., 2017), lomustine (Gustafson and Bailey, 2020), melphanal (Fernandez and Chon, 2018), mitoxantrone (Lucroy et al., 1998), vinblastine (Bailey et al., 2008), and vinorelbine (Wouda et al., 2013), whilst multidrug protocols included carboplatin/doxorubicin (Bailey et al., 2003), carboplatin/5-fluorouracil (Menard et al., 2018), cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) (Vail et al., 2020), cyclophosphamide, vincristine, cytosine arabinoside, prednisone (COAP) (Hosoya et al., 2007), cyclophosphamide, vincristine, prednisone (COP) (Teske et al., 2002; Borgatti Jeffreys et al., 2005), dexamethasone, melphanal, actinomycin D, cytosine arabinoside (DMAC) (Alvarez et al., 2006), lomustine, vincristine, procarbazine, prednisone (LOPP) (Brown et al., 2018), vincristine, doxorubicin, cyclophosphamide (VAC) (Alvarez et al., 2013), and vinblastine/lomustine (Cooper et al., 2009).

Treatment choice was clinician-dependent and based on their discussion with the owners, considering different factors, including tumor type, potential side effects, and costs.

Signalment, tumor type, and disease stage were all documented, as well as protocol type, dosages, number of doses administered, and acute AEs. AEs were divided into three categories: gastrointestinal, hematological, and miscellaneous (hepatotoxicity, cardiotoxicity, and lethargy), and were rated using the Veterinary Cooperative Oncology Group (VCOG) scale (VCOG-CTCAE, 2016). Only those questionnaires that were filled in all their parts were included and used for the statistical analysis.

Statistics was performed using a commercial software (Statistical Package for the Social Sciences 24, IBM Corp., New York, NY). QoL score was measured considering the questions: “Did the QoL of my pet drastically worsen after being diagnosed with cancer?” [Likert scale 1–5; 1 = totally agree (worst QoL), 5 = totally disagree (best QoL)] and “Did the QoL of my pet drastically worsen after starting the chemotherapy protocol?” (same scale). The scores for each question was assessed for normality using the Shapiro–Wilk and Kolmogorov–Smirnov tests, but they both rejected normality. Hence, using the Mann–Whitney U test, the median scores were compared for those groups identified by the possible significant variables: species (dog vs. cat), chemotherapy (single-agent vs. multidrug protocol), side effects (presence vs. absence; hematological vs. others; hematological vs. gastrointestinal; others vs. gastrointestinal), tumor type [mast cell tumor (MCT), LSA, osteosarcoma (OSA), other tumor types]. p-values were considered significant if <0.05.

Ethical approval

All procedures were carried out in accordance with institutional guidelines under the control of the Italian Ministry of Public Health (Italian Law D.lgs 26/2014).

Results

Animals

A total of 101 patients met the inclusion criteria. Patients included 85 dogs and 16 cats; dogs were mostly crossbred (n = 27, 31.8%), followed by Golden Retriever (n = 7, 8.2%), and 4 of each of the following: English setter, French bulldog, and beagle (4.7%); the
Table 1. Questionnaire.

| QoL assessment                                                                 | Never | Infrequently | Sometimes | Frequently | Always |
|--------------------------------------------------------------------------------|-------|--------------|-----------|------------|--------|
| Owner name:                                                                     |       |              |           |            |        |
| Pet name:                                                                       |       |              |           |            |        |
| The person completing the questionnaire lives with the animal:                   | Yes □ |              |           |            | No □   |
| Survey date:                                                                    |       |              |           |            |        |
| I am filling in this form:                                                      |       |              |           |            |        |
| For the first time □                                                             |       |              |           |            |        |
| At a follow-up visit □                                                          |       |              |           |            |        |

Please indicate the category that most accurately reflects your pet’s current health status with a cross for each statement below.

If this is your first time filling in the questionnaire, you should reflect on your pet’s health status over the preceding week. For a follow-up visit, consider your pet’s health over the time period since the last visit.

Joy of life
- My pet has been playing a normal amount for him/her
- My pet has been responding to my presence
- My pet has been enjoying life
- My pet has been happy to see me when I get home

Mental status
- My pet has had more good days than bad days
- My pet has been sleeping more than usual
- My pet has seemed depressed
- My pet has seemed anxious/stressed

Pain
- My pet has been in pain
- My pet has appeared restless
- My pet has seemed painful in the tumor area

Appetite/food intake
- My pet has been eating a normal amount
- My pet has shown a capricious appetite
- My pet has been eating his/her usual diet
- My pet has shown difficulty in eating

Hygiene
- My pet has been keeping himself/herself clean
- My pet’s coat has been in good condition

Gastrointestinal function
- My pet’s defaecation has been normal
- My pet has had diarrhea or constipation
- My pet has been nauseous or has been vomiting

Hydration status
- My pet has been drinking a normal amount
- My pet has been urinating normally

Mobility
- My pet has been moving around normally
- My pet has shown difficulties in getting up
- My pet’s activity level has been normal for him/her

Cardiovascular/respiratory system
- My pet’s breathing has been normal
- My pet has been getting tired easily
- My pet has shown coughing

General health
- My pet has generally been well

Did the QoL of my pet drastically worsen after the tumor diagnosis?
- Did the QoL of my pet drastically worsen after chemotherapy?
- My pet has been having a good QoL.

Comments:
remainder was represented by other breeds ($n = 39, 45.9\%$). The median age was 9 years (range = 3–14 years), gender included female dogs ($n = 47, 55\%$), of which 44 were neutered and 3 entire females, and male dogs ($n = 38, 45\%$), of which 14 were neutered and 24 entire males.

Cats were mostly domestic shorthair ($n = 14, 87.5\%$), followed by Ragdoll and Siamese (one each, 6.25%); median age was 12 years (range = 6–15 years), eight cats were neutered females and eight neutered males.

**Tumor types**
Twenty-seven tumor types were diagnosed (Tables 2 and 3). High-grade multicentric LSA was the most common in dogs ($n = 27, 31.8\%$), followed by cutaneous and subcutaneous MCT ($n = 16, 18.8\%$).

Gastrointestinal LSA was the most common in cats ($n = 4, 25\%$), followed by cutaneous MCT ($n = 3, 18.7\%$).

**Chemotherapy protocols**
When used as a single agent, chemotherapy included the following drugs: vinblastine (17), carboplatin (15), mitoxantrone (6), chlorambucil (5), lomustine (5), melphalan (5), vinorelbine (2), doxorubicin (1), and gemcitabine (1.)

Multidrug protocols were as follows: CHOP (26), COP (7), LOPP (4), VAC (2), DMAC (1), COAP (1), carboplatin/doxorubicin (1), carboplatin/5-fluorouracil (1), and vinblastine/lomustine (1).

**Adverse events**
Of 101 patients, 51 (50.5\%) did not show any AEs, while 50 animals (49.5\%) showed at least one AEs.
Twenty-three (39%) patients experienced gastrointestinal AEs (56% Grade 1, 39% Grade 2, and 5% Grade 4); 29 (49%) developed hematological toxicity, including 22 (76%) neutropenic events (41% Grade 1, 32% Grade 2, 18% Grade 3, and 9% Grade 4), 7 (24%) thrombocytopenic events (14% Grade 1, 44% Grade 2, 14% Grade 3, 14% Grade 4, and 14% Grade 5); 2 dogs (3%) developed hepatotoxicity (Grade 2), 1 dog (2%) had cardiotoxicity (Grade 2), and 4 dogs (7%) developed lethargy (Grade 2).

Eight patients experienced multiple side effects: five (10%) had both hematological and gastrointestinal AEs, one (2%) had gastrointestinal AEs and lethargy, one (2%) had hematological AEs and lethargy, and one (2%) had both gastrointestinal and hematological AEs and lethargy.

When looking for adverse effects at any possible association between QoL and chemotherapy protocol (question: “Did the QoL of my pet drastically worsen after the chemotherapy protocol?”), analysis of the data showed no statistically significant difference between the two groups (single-agent vs. multidrug protocol, \( p = 0.189 \)).

**Significant variables**

The perception of decreased QoL due to the presence of tumor was significantly different between dogs and cats (\( p = 0.026 \)), with a mean score of 2.88 for cat owners and 3.59 for dog owners. Therefore, QoL perception remained positive for dogs, while it strayed into negative for cats.

When adjusting for tumor types, results showed that MCT was the least impacting QoL; the scores were relatively high, namely 4.11 for the first question and 4.16 for the second, showing significant differences (\( p = 0.040 \) and 0.007, respectively) compared with other tumor types.

Prostatic carcinoma, breast carcinoma, nasal tumors, chronic lymphocytic leukemia (CLL), large granular lymphocyte (LGL) leukemia, and high-grade intestinal LSA had the worst scores when assessing data linked to the question “Did the QoL of my pet drastically worsen after being diagnosed with cancer?” On the contrary, tumors with the best score were thyroid carcinoma, MCT, soft tissue sarcoma (STS), and subcutaneous hemangiosarcoma (HSA).

When it came to the second question, “Did my pet’s QoL drastically worsen after starting the chemotherapy protocol?” Dogs treated for pulmonary carcinoma, LGL leukemia, and multicentric LSA had the best QoL score, while dogs treated for MCT, STS, thyroid cancer, subcutaneous HSA, and mammary carcinoma had the worst scores.

To conclude, there were no significant variations in owners’ perceptions of QoL based on the presence or absence of AEs, the type of AEs generated, or the type of chemotherapy protocol.
of chemotherapy (single-agent vs. multidrug regimen) ($p > 0.05$).

**Discussion**

In the last 40 years, we have been faced with a change in the tasks of veterinary medicine and QoL assessment has now become an important component of veterinary oncology, both in clinical research and during the daily clinical assessment (Belshaw et al., 2015), with an exponential increase in the number of published articles about this topic (Mellanby et al., 2003; Tzannes et al., 2008; Lynch et al., 2010; Vøls et al., 2017). In human medicine, protocol’s choice is mainly based on reported treatment response, expected toxicity, patient preference, disease stage (e.g., advanced disease or presence of metastases for solid tumors), or imminent complications requiring aggressive and rapid tumor control (Grünberger et al., 2007; Kumar and Chakraborty, 2016; Petrelli et al., 2020).

Several studies in human medicine have shown that multidrug versus single-agent protocols are associated with improved overall survival and response rate without necessarily worsening QoL (Funaioli et al., 2008; Yalcin et al., 2020), which appears to be unrelated to the toxicity profile of the specific protocol (Funaioli et al., 2008).

Also, in veterinary medicine, especially when analyzing the available literature on multicentric LSA treatment, multidrug compared to single-agents protocols have been associated with increased response rate and overall survival (Valerius et al., 1997; Al Nadaf et al., 2018); nevertheless, we tend to choose the type of chemotherapy based on several factors, including tumor type, type and interval of administrations, expected AEs, owners’ acceptance of potential side effects and costs.

The major goal of our study was to determine how owners felt about their dogs’ QoL while they were receiving an MTD protocol, whether it was a single-agent or a multidrug protocol, and to uncover clinical characteristics that may be linked to a drop in QoL. No significant differences were found when considering the presence or absence of AEs, type of developed AEs, and the chemotherapy protocol used (single-agent vs. multidrug protocols). Therefore, based on these data, the chemotherapy protocol of choice should be merely based on medical considerations, rather than concerns regarding the consequences of owners’ perception of QoL.

Half of the patients (51%) in both groups did not show any toxicity when considering side effects. All the VCOG toxicity grades, ranging from 1 to 4, were included in the study but, due to low numbers, types, and grades of AEs in different groups (e.g., hematological, gastrointestinal, others), could not be statistically compared and associated to their impact on QoL. A correlation has been reported in human medicine where the severity of chemotherapy-related AEs, mainly classified as grade 3 or above, were strongly correlated with the QoL of patients with advanced cancer (Park et al., 2016). Regarding the species, the perception of decreased QoL following the cancer diagnosis was significantly different between dogs and cats, and QoL perception remained positive for dogs while strayed into negative for cats. The varied habits and behavior of dogs versus cats, as well as the varying time spent by the owner in the indoor and outside environment with their pet, might be a plausible reason for this outcome.

When looking at specific tumor types, our study found that LSA did not seem to affect QoL: this is in agreement with previously reported results in both dogs and cats, where the QoL of LSA patients was not affected (Mellanby et al., 2003; Tzannes et al., 2008; Thornton et al., 2018).

MCT was the tumor to be least impacting QoL; this is not surprising since most patients included in the study received adjuvant chemotherapy with vinblastine to treat microscopic disease. Furthermore, OSA had no negative impact on QoL; one possible explanation for this finding is that most OSA patients had already undergone limb amputation and were thus pain-free when chemotherapy treatment began; however, due to the small number of cases, we are unable to draw any meaningful conclusions from this data. Prostatic carcinoma, breast carcinoma, nasal tumors, CLL, LGL leukemia, and high-grade intestinal LSA were among the tumors with the worst scores, which is not unexpected given that chemotherapy was used as a palliative treatment or as the sole therapeutic option.

In the present study, a wide number of tumor types was included: again, as a consequence of the lack of numerosity in the single groups, data concerning the correlation between tumor type and QoL should be interpreted with caution.

This study has several limitations, including the absence of a validated method to assess QoL in veterinary oncology patients. Many reviews have focused on the validation of different methods used to measure QoL (McMillan, 2000; Wojciechowska and Hewson, 2005; Giuffrida and Kerrigan, 2014; Belshaw et al., 2013; Vøls et al., 2017) and, even if recently Giuffrida et al. (2018) proposed a psychometric test to standardize the measurement of QoL, tools to measure QoL in pets suffering from cancer need to be validated in the future. One of the significant differences between human and veterinary medicine in defining patients’ QoL is that, in human medicine, this parameter is, in most cases, stated by the patient himself. On the contrary, veterinary medicine is determined by the owner or, alternatively, by the clinician or both (McMillan, 2000). Additional QoL evaluation domains in addition to the classic clinical and physical parameters have been added to our questionnaire, as previously reported by Vøls et al. (2017), and should be routinely considered in the assessment of QoL in veterinary patients, based on...
models such as the PedsQLTM scale designed to assess QoL in children (http://www.pedsqol.org). The low number of patients represents another limitation of the study included in each subgroup and the heterogeneity of our groups in terms of tumor types and chemotherapy protocols used; for this reason, patients could not be stratified based on the type or combination of used drugs and the degree of recorded side effects; also, a potential association between tumor characteristics (tumor type, disease stage) and owner’s perception of QoL could not be investigated further. Also, the questionnaires were not anonymous, and it is possible that anonymous answers could have increased the chance of retrieving scores with a more negative trend. Finally, this study included only a referral population, thus creating a bias regarding the type of cases and owners that could have shown a higher motivation and were possibly more willing to accept and tolerate chemotherapy AEs.

To conclude, our study suggests that type of chemotherapy protocol and related AEs did not affect owners’ awareness of their pet QoL. Therefore, a multidrug protocol appears to be well tolerated by the owners of pets undergoing chemotherapy. It should be discussed and offered more often, independently of the perceived influence of potential AEs on QoL.

Future prospective studies looking for clinical factors possibly related to QoL, such as species, age, tumors histotypes, stage of the disease, and intent of the protocol (curative vs. palliative), are warranted. Possible factors related to QoL, such as species, age, tumors histotypes, stage of the disease, and intent of the protocol may be possibly related to QoL. Possible factors related to QoL may be identified in future studies.

**Conflict of interest**
None of the authors has any other financial or personal relationships that could inappropriately influence or bias the paper’s content.

**Authors’ contribution**
MLB and PV conceived and supervised the study; DD performed statistical analysis; ET supervised the study, was directly responsible for the clinical cases, and assisted during data collection. CC, VA, and IB were directly responsible for the clinical cases and assisted during data collection.

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