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PLANNING FOR SUCCESS IN CHEMOTHERAPY

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“Chemotherapy doesn’t work for my patients”
“What’s the point, you’re just delaying the inevitable”
“I gave chemo to a dog, and it died from the treatment”
“My clients just don’t want to put their pets through more pain and suffering”

These are defeatist statements, but they are based on experiences, misconceptions or lack of knowledge. This educational segment will give some useful tools to improve on past experiences, address misunderstandings (vet or client) and point you in the right direction to address specific areas of knowledge.

**Does chemotherapy work?**

If I asked you “does amoxicillin/carprofen/imidacloprid/furosemide/etc work” you would undoubtedly answer YES! Of course, these drugs (and many others) only work when used at the correct dosage, route, duration and the correct diagnosis. Carprofen doesn’t alleviate lung oedema, and furosemide has no analgesic properties. A patient would benefit from furosemide on the basis of a history, clinical examination, radiographs, some pre-treatment blood tests and an echocardiogram giving a diagnosis of congestive heart failure due to, say, mitral valve insufficiency. The patient with CHF is never going to be cured, will deteriorate, require checkups (blood, urine, radiographs, etc) and will certainly suffer from treatment side effects. Some are minor (e.g., pupd) others quite serious (e.g., renal failure, hypotensive syncope etc). But no vet ever hesitates to treat CHF. Now, every year about 1.2 million cases of cancer are diagnosed in humans in the USA; TWO THIRDS go on to full and durable remission. The survival rate and time of canine OSA (osteosarcoma) has improved sixfold in thirty years; the 3-year remission rate for lymphoma with chemoradiation protocols is 34%; and 88.5% of grade II mast cell tumours can be cured by chemoradiation. Those odds are better than the cure rate of arthritis, Cushing’s disease, Diabetes Mellitus, renal or heart failure = 0%
So once you accept this, you have to ask yourself which patients can be cured and which cannot. I think this is very important, certainly more important than which protocol to use. How do I make the decision what to advise? I collect information! You need to know:

1. WHAT TUMOUR you are dealing with (or if it’s even a tumour!)
2. HAS IT SPREAD to the local lymph nodes?
3. HAS IT SPREAD to any other organs?
4. Are there any CONCURRENT ILLNESSES or considerations?

This is what I call the TNMD system, a modification of the TNM (tumour-node-metastasis), adding “DISEASE”. It makes no sense to be heroic and do surgery for a mast cell tumour, embarking on months of chemotherapy, and ignore the patient’s chronic, unremitting hip arthritis. So how does the busy GP collect this information?

1. HISTORY – take a detailed history including:
   a. Appetite, Drinking, Vomition, Diarrhoea, Faeces and Urination; Lamenesses; Scratching or skin complaints; Coughing, sneezing or breathing problems; pain
   b. For lumps, make sure you ask about the rate of change – but beware, some mast cell tumours will hang about for 2-3 years and feel exactly like a lipoma!

2. EXAMINATION – pay particular attention to the mucous membranes and skin for petechiae, ecchymoses, depigmentation, primary oral masses; ALWAYS do a rectal, to evaluate the perianal skin, anal glands, rectal mucosa, sublumbar lymph nodes and prostate/bladder.

3. URINE – proteinuria, lack of concentration ability, sediment with bacteria or strange cells

4. FINE NEEDLE ASPIRATE – if the suspect is superficial, ALWAYS FNA! Use a 21g, 1¼” needle attached to a partially evacuated 5ml syringe. Spray and spread onto a slide, and as long as the hub and chamber of the syringe are not blood-contaminated, you can reuse the syringe with a new needle, to make a second slide. If a dog has 13 lumps, make a “dog map” and a MINIMUM of 26 slides! Check each one, and if there is no decent cellular material, do it again. If you cant get cells, consider using an 18g needle, or an incisional biopsy. DON’T ASSUME! Of course, all this can take time, so a patient with multiple lumps should be admitted and worked up at leisure, and thoroughly.

5. FAECES – most vets forget this one, but Spirocerca lupi eggs in a dog with lungs mets could be significant, and endoparasites provide a portal for bacterial translocation in patients on chemotherapy

6. BLOOD PROFILE – you have to have baselines before treating with myelosuppressive drugs, or you have no business giving them. Similarly, for renal and hepatic function. Many of these drugs are metabolised and excreted by hepatorenal mechanisms. You give vincristine, one of the most commonly-used chemos, at your own peril, if you are not aware that any degree of hepatic impairment can be fatal for patients injected with this drug. Similarly, albumin carries these drugs around the body. Many neoplasms affect blood calcium,
and calcium and old age (most cancer patients are >7 years old) affect phosphate – so TEST DON’T ASSUME. In some instances, blood testing can be helpful in prognostication, for example, hypercalcaemia is a negative prognostic indicator for lymphosarcoma,(Legendre, 2007) and an elevated ALP in a patient with OSA halves the median survival time from 400 days to about 170d(Chun & Lorimier, 2003).

At this point, you’ve probably spent about R1000 – R1500($150-$250) of your client’s money, and discovered a whole lot. A clean bill of health is not a waste of money- it means you can proceed with more confidence that you aren’t going to be caught out by a preventable calamity! Now that you know this, extend your database. You should already have some clues about the identity of the culprit. If you are unsure, send them to a veterinary cytologist.

**EXTENDED DATABASE**

**Radiographs**

In my personal experience, one of the biggest weaknesses of staging by GPs lies in taking only 1, poorly-exposed, poorly-position thoracic radiograph and thinking that this is adequate. IT IS NOT. Many tumours spread metastasise to the lungs. It is important to know which ones spread to the lungs, and which don’t. For example, SCC (squamous cell carcinoma) of the nose, eyelids and pinnae of cats spread extremely late, and MCT rarely spread to the lungs.

Good radiographs require a high kVp (70 + 2 x thickness in cm), and a low mAs (2). The forelimbs must be drawn well forward, clear of the cranial mediastinum, and the radiograph taken at peak inspiration. Two lateral views (marked according to the side on the table) and 1-2 VD/DV rads are required.

**Ultrasound**

If your practice has US capabilities, then abdominal US may be important to evaluate the liver, spleen, kidneys and intraabdominal lymph nodes. You can also do US-guided FNA of suspicious masses. US can also help corroborate clinical pathology findings.

**Biopsy**

Never, ever, do an excisional biopsy when the results of the biopsy might influence the course of treatment. For example, a poorly-performed (narrow or incomplete “shelling out”) of a soft tissue sarcoma or mast cell tumour will almost certainly doom a patient to death; a small incisional, punch or tru-cut biopsy will diagnose the tumour, and allow curative-intent radiation therapy for only slightly more cost.

**Helping the client understand the options**

One of the most important aspects to carrying out successful chemotherapy is that the decision to treat is NOT yours, but the owner’s. The owner can only make the correct choice for him or herself, if he is presented with the right information, conveyed concisely and with simple clarity. This means you need to have this information, have time to collate and crystallise it, and if necessary, get the advice of a specialist physician, surgeon, pathologist or clinical pathologist.

If a patient has comorbidities, then start by informing the client of these, and discussing their relevance to the patient, before dealing with the neoplasm. Show them how you can help manage more than just the tumour,
and improve the patients ENTIRE QOLS (quality-of-life spectrum). For example, the patient who has a splenectomy and is receiving doxorubicin for a haemangiosarcoma, but who also suffers from arthritis and chronic otitis externa, should also be on a chondroprotectant, NSAID and an ear-cleaning regimen eg Otoclean. The 13-year-old Maltese about to undergo carboplatin chemo for an excised carcinoma should have a thorough dental prophylaxis prior to starting chemo, if the teeth are vrot.

Once you have dealt with these additional issues, present the client with options:

1. THE TUMOUR IS EXTREMELY CURABLE (>80% cure rate)
   a. Mast cell tumours
   b. Some SCC
   c. Mammary tumours <4 cm

2. THE TUMOUR IS POTENTIALLY CURABLE but long-term palliation is the norm
   a. Lymphoma
   b. Osteosarcoma

3. THE TUMOUR IS PALLIABLE
   a. Splenic haemangiosarcoma

4. THE TUMOUR IS INCURABLE but relief from symptoms is possible

5. DEATH AND SUFFERING without imminent euthanasia
   a. Ruptured splenic haemangiosarcoma with metastases or atrial primary
   b. Brain neoplasm with status epilepticus
   c. Neoplasia with organ failure / insufficiency obviating treatment
   d. Cardiac tamponade

I think far too many animals are not treated because the vet doesn’t know what can be achieved, or doesn’t refer the patient after a thorough investigation which opens up the options, which include referral to a specialist, or getting the advice of a specialist. Radiotherapy and highly myelosuppressive chemotherapy are always an indication for referral, but that still leaves a large scope for treatment by GPs. Putting a patient into one of the above 5 classes can help enormously in deciding how to treat a patient.

In order to understand what treatments are available to a patient, first you must know what you are dealing with, and its extent; secondly how comorbidities preclude certain treatments; and thirdly, how treatment of comorbidities (eg dental, atopic or arthritic disease) may complicate or liberate chemotherapy.

**Side effects of chemotherapy**

Knowing the side effects of chemotherapy drugs you intend using is an absolutely crucial prerequisite for using these drugs. The main side effects may be minor (requiring no or only symptomatic management) or major (requiring hospitalisation and/or investigation).
<table>
<thead>
<tr>
<th>Drug</th>
<th>Myelosuppression</th>
<th>GI effects</th>
<th>Renal-Urinary</th>
<th>Hepatic</th>
<th>Skin/Tissues</th>
<th>CNS</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vincristine</td>
<td>Mild*</td>
<td>Constipation</td>
<td>Excreted 7d</td>
<td>Metabo-lised</td>
<td>Vesicant</td>
<td>Neuro-pathy</td>
<td>Thrombosis, Infection, Pancreatitis, Diabetes</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>None</td>
<td>Ulcer-ation</td>
<td>UTI, renal failure</td>
<td>Steroid hepato-pathy</td>
<td>Cushing's</td>
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<td></td>
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<tr>
<td>Cyclophosphamide</td>
<td>Moderate-Severe 7d</td>
<td>CINV</td>
<td>CRF, Haemorrhagic cystitis</td>
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<td></td>
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</tr>
<tr>
<td>Doxorubicin</td>
<td>Moderate 7d</td>
<td>CINV</td>
<td>ARF in cats</td>
<td>Metabo-lised</td>
<td>Vesicant</td>
<td>Cardio-toxicity</td>
<td></td>
</tr>
<tr>
<td>Carboplatin</td>
<td>Moderate 14-21d</td>
<td>CINV</td>
<td></td>
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<tr>
<td>L-Asparaginase</td>
<td>None**</td>
<td>Affects VCR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Thrombosis, Pancreatitis</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>Moderate – Severe 7d</td>
<td>Constipation</td>
<td>Metabo-lised</td>
<td>Vesicant</td>
<td>Neuro-pathy</td>
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</tr>
<tr>
<td>Chlorambucil</td>
<td>Mild 7d</td>
<td>CINV</td>
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UTI = urinary tract infection; CINV = chemotherapy-induced nausea and vomiting

*severe if co-administered with L-asparaginase
**severe if co-administered with Vincristine

**Monitoring chemotherapy**

If you are going to administer a drug, and you know its side-effect profile, then you must monitor it to check that you are neither over- nor under-dosing treatment. I usually monitor myelosuppressive drugs at the nadir point, using my in-house haematology analyser and a manual blood smear, just prior to chemo. This is the ideal way, but you can use an outside laboratory, although the delay means clients must make extra trips. An alternative is to manually evaluate a blood film (K. M. Wyatt & G. L. Wyatt, 2002) although a full differential count is required. In this technique, dogs with <100 neutrophils per low power field (100x) were considered to be neutropaenic, and those with >100/LPF were deemed to have adequate neutrophils. In the same article, at 1000x magnification with a 0.18mm field of view, patients with <1000 thrombocytes per 10 HPF were considered thrombocytopaenic.

If you are administering doxorubicin, you must ensure that your patient can have periodic echocardiography performed by a properly trained radiographer or physician to detect early signs of dilative cardiomyopathy. If administering doxorubicin to a cat, check renal function with urea, creatinine, phosphate and urine sg and protein. Carboplatin patients should have creatinine and haematology performed prior to each treatment. Dogs and cats receiving cyclophosphamide are at risk for haemorrhagic cystitis; educate clients on what to watch for, even given them dipsticks to check for spotting. CPP-associated sterile haemorrhagic cystitis develops in 9% of dogs receiving CPP, whereas only 1.2% of patients receiving it concurrently with furosemide develop it(Charney, Bergman, Hohenhaus, & McKnight, 2003). Patients on L-asparaginase should have physical

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examinations for ecchymoses and petechiae. It is irresponsible, as a medical professional, to administer chemotherapy without doing the proper follow-up. I always ask myself, how would I like to be treated by my (human) medical professional, if I had cancer? I hope with respect for me as a patient deserving of the best treatment I could tolerate and afford.

Before blaming the chemotherapy for any side-effect, ask yourself if a patient is sick because of the disease for which it was presented, one of the comobidities you uncovered during initial investigation (or their treatments), another comobidity, or because of some inherent problem with the patient.

In the lecture, we will discuss proactive planning and evaluation to decide on the appropriate treatment for patients prior to initiating therapy, to achieve the best results possible.