Understanding Cancer Chemotherapy

In honor of Evie, the brilliant guide dog who succumbed to lymphoma when she was not yet 5 years old.

Gil is one of my most devoted listeners. He is blind and has had a succession of guide dogs for 25 years. He recently discovered that his Black Lab Evie, who was barely five years old and the most beloved of all his guides, received the terrible news that she had lymphoma. She died within a week of receiving chemotherapy and Gil could not understand how this happened. I wanted to help answer some of the medical/oncological questions so as to give him some peace of mind and allow the grieving process to proceed.

Gil came to me because he believed that her sudden death appeared to have been caused by the chemotherapy drug Elspar used in conjunction with Oncovin -- perhaps administered incorrectly, since he had been told she was a great candidate for treatment because she was otherwise in supremely good health. I needed to help him understand what happened that ended the life of his young and brilliant guide dog. This is more than the loss of a beloved pet, although Evie was all that to him, as well. This dog was such a valuable asset and worker that she traveled with him over 100,000 air miles all over the world to help foster independence for the blind with hand held GPS systems. Her talent and work ethic were invaluable to him and coming to grips with what has occurred required more information than his own vets gave him. Gil wanted to get peace of mind for himself, but also hoped that whatever we learned might help other people in similar situations. I turned to two of the smartest people I know: veterinary oncologist Dr Brian Huber, who runs the chemotherapy company Oncura Partners, and Dr. Donna Spector, a board certified veterinary internist and the Official Second Opinion Vet of my radio shows.

Gil's dog Evie had been in excellent health except for a day of vomiting, after which Gil felt her all over and discovered that she had enlarged lymph nodes in the groin area. He went that day to his vet who did a needle biopsy showing lymphoma. He then went to the Animal Cancer & Imaging Center (ACIC) in Michigan for an evaluation. That biopsy showed multicentric lymphoma (B cells) stage 111a.

The examining vet said the dog's heart, lungs and body condition were all excellent and made her a great candidate for chemo. They quoted an 8-14 month remission after the first treatment and that further treatments could gain longer amounts of time, but predicted that this dog would exceed the first predicted time.

Because of travel time, Gil elected to have his own vet administer the Univ. of Wisconsin at Madison protocol, which was sent to him and the vet by ACIC, and is considered the standard treatment universally used for lymphoma. After the IV administration of Oncovin, Evie's white blood cell looked good 3 days later. She had no fever and the lymph nodes had returned to normal size and were no longer swollen enough to measure. She had responded very well to the chemo. At this point, the Elspar was administered,

and Gil now wonders if that was the correct protocol? Could it have been lethal? Because 5 days later Evie suddenly became deathly ill -- 104 temp, drinking profusely, no white cells at all in her blood -- and she was dead within hours.

When Gil called to get information, what he heard distressed and confused him. The Vet Tech at ACIC told him (incorrectly as it turns out) that ACIC "did not use the U of W protocol, they never used Elspar in the first treatment, only used it later in the protocol as a rescue drug if things were not progressing well." Gil's own vet could not explain Evie's sudden death. She also did not give him confidence, in retrospect, that she had known what she was doing every step of the way.

Dr. Brian Huber's reply:

From your comments I am suspicious of *acute tumor lysis syndrome* -- it is not common, but an emergency when it does occur! But realize all my comments are generalizations, as I have NOT seen patient, nor the blood tests or Staging tests for this cancer patient. I am ONLY going on what you provided (and this might be inappropriate information if I had more patient data available).

As far as the Univ. of Wisconsin Lymphoma protocol -- the current standard in the industry is to use the Elspar in the UW Short Course lymphoma protocol. Elspar and Vincristine (Oncovin) are often used together on the same day in a healthy patient or separated by 48-72 hrs in a sicker type patient beginning chemotherapy. Sometimes the reason some facilities have not been including Elspar is because of the previous shortages in the market, and they got used to doing without! There was one study that questioned the use of Elspar in first line chemo for Lymphoma, but it is still being used MORE than not.

A patient can have a severe allergic reaction to Elspar therapy -- but this is most common on the second or third time Elspar is used in a patient, not the first time, so I doubt that was the cause of the sudden decline.

There MIGHT have been a delay in identifying the pets condition post chemotherapy -- especially if the veterinarian did not have immediate access to the oncologist, or the pet owner just assumed the pet was feeling bad due to the chemotherapy only and was not informed of the signs and symptoms of ATLS, which is what I suspect was the cause of her decline. The description of it follows, but basically it happens in dogs whose cancer responds very well -- too well and too quickly -- to the chemotherapy so the cancer cells all die off at once and the body is overwhelmed by having to cope with eliminating it all.

1. **What is acute tumor lysis syndrome? Is it a life-threatening emergency?**

   Acute tumor lysis syndrome (ATLS) is a condition of acute collapse that may lead to death soon after administration of a chemotherapeutic agent to an animal with a chemosensitive tumor. Although uncommon, it certainly presents an urgent situation. In short, chemotherapy results in the acute death of large amounts of

tumor and release of cellular contents that may be acutely toxic. This emergency situation is under recognized in veterinary patients and is becoming more common with the widespread use of chemotherapeutic agents. Therefore, when a case is suspected, a complete history and physical examination is taken as an intravenous catheter is placed and blood samples are obtained for subsequent analysis.

In dogs and cats this syndrome has been associated with lymphoma and leukemia. ATLS may occur after effective chemotherapy in animals with rapidly growing, bulky, chemosensitive tumors. The patient often is presented with a history of acute decompensation over a short time -- sometimes to the point of imminent death. Rapid diagnosis and therapy are essential to reduce mortality rates.

2. **What factors predispose animals to ATLS?**

Rapid tumor lysis may cause acute release of intracellular phosphate and potassium. This release of electrolytes causes hypocalcaemia, hyperkalemia, and hyperphosphatemia. Hyperuricemia is also seen in people, but this is not a concern in veterinary patients.

ATLS is most common in animals with some degree of volume contraction and a large tumor mass that responds rapidly to cytotoxic therapy. In addition, septic animals or animals with extensive neoplastic disease that infiltrates the parenchyma are predisposed to ATLS. Veterinary patients at highest risk are volume-contracted dogs with stage IV or V lymphoma that are treated with chemotherapy and undergo rapid remission. ATLS is most often identified within 48 hours after the first treatment.

3. **How is ATLS diagnosed?**

When ATLS is suspected, the history should document the recent administration of chemotherapy to a pet with lymphoma, leukemia, or other chemoresponsive tumor. A rapid, thorough, and complete physical examination should be performed to identify telltale signs of cardiovascular collapse, vomiting, diarrhea, and ensuing shock. The accompanying hyperkalemia may result in a bradycardia and diminished P-wave amplitude, increased PR and QRS intervals and, rarely, spiked T waves on electrocardiogram. Biochemical analysis of blood may confirm the presence of hypocalcemia, hyperkalemia, and hyperphosphatemia. In the presence of elevated serum phosphate levels, hypocalcemia develops as a result of calcium and phosphate precipitation. Without effective treatment, renal failure may occur; therefore, concentrations of blood urea nitrogen and creatinine should be monitored closely. Fluid therapy should be initiated as soon as an intravenous catheter is placed.

4. **What is the treatment for ATLS?**

> The ideal treatment is prevention. Identify predisposed patients that have heavy tumor burden, a chemoresponsive tumor, and volume contraction. Because the kidney is the main source of electrolyte excretion, metabolic abnormalities may be exacerbated in the presence of renal dysfunction. Identification of patients at risk and correction of volume depletion or azotemia may effectively reduce the risk of ATLS; chemotherapy should be delayed until metabolic disturbances such as azotemia are corrected.
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> If ATLS is identified, the animal should be treated with aggressive crystalloid fluid therapy. Further chemotherapy should be withheld until the animal is clinically normal and all biochemical parameters are within normal limits. The fluid rate should be adjusted to meet the needs of each patient, as directed by monitoring of body weight, heart and respiratory rates, central venous pressure, ongoing losses such as vomiting and diarrhea, and urine output.

I then replied to Dr. Huber and his replies are italicized:

Dear Brian -- I am really grateful for your swift reply, and fully understand that I gave you only bare details so your responses are taken with that in mind. Gil felt that a gross error may have been made in dispensing the Elspar at all. From what you say, that is not the case and also there was a 3 day wait before administering it the first time.

Elspar IS indicated in the vast majority of Lymphoma patients. The discussion around to use or not to use is ongoing! Like I said before, you will find as many that do use it in the initial protocol step, and about equal number of oncologists that now wait to use it for dogs that come out of remission. I can say with confidence that we will always want this drug in our therapies because of its effectiveness in decreasing the Lymph node sizes (internally as well as the nodes on the outside that pet parents see). The challenge is to properly evaluate the patient in front of the Dr at the time. There is no one ideal protocol or drug for any patient (side effects are usually very unpredictable) or the patient's cancer. We like to think that we can neatly classify how patients respond and what their long-term prognosis should be, however, after working with oncology pet patients over 20 years I can say this is just not the case.

For my own education, and to pass on to others, is ATLS something that can be predicted?

NO! That is the frustration; it is mostly seen in pets with large tumor burdens of HIGHLY responsive cancer like Lymphoma (particularly). Even with the large tumor burdens the vast majority of pets do NOT develop ATLS. I can say that ATLS does not always read the book, meaning I have seen it reported as much as 5-7 days post chemo (especially the Elspar and Vincristine dosing on first cycle of this protocol.

Was there some level of vigilance the dispensing vet should have/could have exerted to catch this reaction sooner?

Maybe, but there must be a complete evaluation at the time the pet is acting sick -- a full comprehensive blood panel, blood gases and IV Fluids -- aggressive therapy is needed. Again, many doctors assume that what is happening is a "normal" post-chemo reaction and then pet is crashing when actually brought back into hospital.

Evie was eager to play, chasing a ball, entirely "healthy" -- and then crashed, but she had been given the Elspar five days before, so now it leads me to think her sudden death was caused by ATLS. Once there is an ATLS reaction, is it somewhat irrelevant how quickly you respond since the reaction has already taken place?

No, if caught in the stages of electrolyte abnormalities and patient is supported with proper therapies -- most of these pets will survive this crisis. Most then go on and continue treatment protocols.

Meaning that if she had gotten into the vet immediately when symptoms appeared -- and the vet had recognized it as ATLS and jumped right on it, there could have been a chance to pull her through. Personally, I think it is best to stay with your own vet after cancer diagnosis and let them handle the treatment, but only if Oncura Partners were supplying the protocol and medications for the treatment -- and then there is 24 hour back up for the vet. I believe this is your business model: pets can stay closer to home, be treated by familiar doctors, but they in turn don't have to second guess anything because Oncura has done the planning for them and provides emergency advice, as well. It is what I would have recommended to Gil if I had been involved sooner.

In a way yes, but we do need family doctors that are willing to be involved with patient care to this level. (As you may know, there is a wide variance of doctor abilities and desires to practice the higher level of medicine -- in veterinary and human fields.) What we do provide with Oncura Partners is the Oncologist interaction on all case decisions and therapies. We have an emergency management system in place that would have walked this doctor through steps of management and testing needed right away. These Emergency cases go to the top of review and alert to our Oncologists to respond to immediately. This does not always guarantee great outcomes -- but it does allow patient care to be as seamless as possible and we have tried to cover all the "Unexpected" potentials for oncology case management. Oncura Partners is finalizing the integration of "PhaSeal" closed administration system products. This is the best safety system for hospitals now available (Human or Vet). This is not a direct issue for Pet parents -- but increases the potential comfort level of Veterinarians considering offering cancer management services to their clients.

Thank you for your time and wisdom, Brian. I also want to say that this is another reason that pet insurance is essential because we know cancer is widespread -- and in this case, lymphoma is the most prevalent kind of cancer. I am grateful to Jack Stephens not just for introducing me to you, but for founding Pets Best insurance because otherwise people would go bankrupt diagnosing and treating cancer (or not even be able to embark on it,

with all the attendant guilt and sorrow). As you know, Pets Best pays 80% of the bills, including a second opinion vet, whom I would also have recommended to Gil.

*I then shared all this correspondence with Dr Donna Spector, who I believe would have been able to work with his vet (by phone and/or email) and given that doctor and Gil the information, advice and emotional support to get the best possible care for Evie. Here are Dr. Donna Spector's comments in **bold**:*

Although Elspar may not add to the length of the initial remission it is often used in dogs that are not feeling well with their cancer because it works so quickly. If my own dog was suffering from lymphoma and was vomiting, not eating and generally feeling crappy I would want a drug that could help turn that around quickly and Elspar is capable of that. If a dog like Evie is feeling fine and dandy with their lymphoma just enlarging their lymph node then maybe I would consider holding on to Elspar until later on. It is very dependent on the dog and how it is feeling on the day of diagnosis/treatment.

I understand that this gentleman is really questioning the handling of his dog but when it comes to Elspar there really isn't a right or wrong way to use it and the more opinions he seeks will just muddle the issue for him. You would have oncology specialists argue on both sides of this "to use" or "not to use" Elspar coin so it is tough to say it was used "incorrectly." Currently it is still listed in all protocols as an initiation drug. Also the ultimate signs this dog developed are not likely due to Elspar, like the low WBC (white blood count) and fever are not consistent with Elspar side effects as it does not suppress the bone marrow -- that most likely came from the Vincristine (Oncovin). If this dog had an excellent response to Vincristine and all lymph nodes were already decreased in size the tumor lysis (destruction of the tumor cells) had started before Elspar was ever given. So whether it was used or not used may be a moot point it may not have even been the problem in this particular dog.