Murray Shaw: Cancer is My Hobby

As someone living with an “indolent” cancer (slow to develop, treatable, but so-far incurable) for the last dozen years, I have decided that the best way for me to think of it is as a hobby. It is fascinating, time-consuming and important to me, but, like all hobbies, should not become an obsession. Like any other hobby, it can be referred to briefly to tell people how I’m doing, but should never be dwelt upon in normal conversation. As key treatment decision points approach, I focus on catching up on the literature, but between times I put it into the back of my mind and get on with as normal a life as possible.

The following story outlines how my “hobby” developed and how it has progressed:

My involvement with cancer started out as a textbook case of what not to do. As a male with a highly demanding executive job, I had put off having one of the company-provided medical examinations for a number of years, since I was a marathon runner and seemed to be in fine shape. The year I turned 57 (2002), the company experienced a hostile takeover. I was retained to help with the transition to the new team and then let go, like all the rest of the previous management team. Since they wanted to reward my assistance to them, they gave me a handsome set of retirement benefits. Finally showing a bit of common-sense, I insisted that they include my long-postponed medical check-up. The examination turned up colon cancer at a late enough stage to require immediate surgery, with a bowel resection. The surgery did succeed in removing the cancer entirely. Another year of avoidance would have been fatal.

Over the next two years, as I recovered from the operation, we moved from Connecticut to Chicago to Zurich and, finally, back to our long-term home in Ottawa. During this period, I found that my running training gradually seemed to become more and more difficult, and I became convinced my stamina was decreasing. So, on our return, I sought out a new GP and underwent a battery of tests. The key indicator seemed to be my hemoglobin levels, which obstinately remained a bit below normal despite a healthy diet and lots of exercise (including a three-week wilderness canoe trip). With admirable persistence, the GP sought specialist advice from a hematologist/oncologist who, in 2004, diagnosed an uncommon form of non-Hodgkin's lymphoma called Waldenstrom's macroglobulinemia (WM).

This struck me as one of the divine comedy's funnier gags. There is an ancient Greek saying, "those whom the gods would destroy, they first make proud." Having spent 54 years of my life priding myself on competitive stamina athletics, which depend upon developing high levels of hemoglobin, it is rather ironic that my form of cancer's main effect is to drastically reduce hemoglobin levels.

Although my hemoglobin continued to slowly decline, it remained at an acceptable level for several years, so we went into watch-and-wait mode – which, more realistically, felt like "wait-and-worry" – while we tracked my blood chemistry and researched recent developments in the treatment of WM.

As someone with a Ph.D. in chemistry as well as one in biochemistry, I read up on the literature during this period and sought out support groups. It is amazing how much information there is on the web, in this case including a lead to the IWMF with a Canadian affiliate, WMF Canada, which has a local support group in Ottawa. I found the IWMF's online forum to be an excellent "talk-list" containing questions, answers and experiences from hundreds of WM patients and medical specialists worldwide. I also had the benefit of friendship with my chemistry professor's son, who had established himself

as a hematologist specializing in lymphomas and leukemia at the Mayo Clinic, and was therefore a source of exceedingly helpful advice.

While awaiting the moment when I would need to select my first treatment (out of three or four preferred options), one principle predominated: although my hematologist/oncologist was very willing to discuss treatment options and listen to my findings, I knew it was essential to establish a relationship where I entrusted the final decisions to her. That relationship has developed into a friendship over the last thirteen years, and is based on my enduring respect for her broader knowledge and experience. I have more time to concentrate on WM – which is only a small portion of her practice – and she appreciates and considers my findings and analyses. But our relationship would not have flourished without my fundamental respect for her final judgements.

With WM, there are really two key areas of concern: hemoglobin and immunoglobulin levels:

1. The critical level for hemoglobin is about 10.0 g/dL (the normal range for males is about 13.5 to 17.0 g/dL), below which there begins to be an oxygen transport deficiency. At lower levels, it affects daily life and health through a decrease in stamina and an increasing tendency to become light-headed to the point of collapse on minor exertion.
2. The corruption of immunoglobulin production presents two problems:

- The cancerous cells produce large amounts of identical copies of a giant immunoglobulin molecule (IgM) that is not only useless as a component of the immune system, but also increases blood viscosity. In some case it also attacks the myelin sheath of peripheral nerves, producing pain and numbness called “peripheral neuropathy” (PN). The PN often is accompanied by heavy “night sweats”.
- The cancerous changes resulting in monoclonal IgM proliferation also suppresses the production of other key “good” immunoglobulins, which can lead to increased susceptibility to disease.

By 2008, my hemoglobin was about to fall below 10.0 g/dL, and my IgM level was high enough to be causing heavy night sweats and painful PN, so we selected my first set of treatments.

At that time, there were two traditional options:

1. Nucleoside analogues – a set of chemotherapy drugs that substitute for one of the four key nucleotides and therefore inhibit DNA production in all fast-growing cells (examples: cladribine and fludaribine).
2. An alkylating agent that directly attacks DNA in all fast-growing cells by forming cross links which prevent its replication (example: **c**yclophosphamide). In its most effective use it was combined with **h**ydroxydaunorubicin, which inserts itself between DNA bases, **O**ncovin which directly interferes with cell replication and **p**rednisone a corticosteroid. The combination, called **CHOP**, was by far the preferred treatment from the mid-1990s on.

There was also a new drug just emerging from clinical trials but obtainable only on special application: a monoclonal antibody, rituximab, which binds to a unique surface feature of WM cells called CD-20, and aids the immune system in attacking the cancerous cells.

When rituximab was first introduced it was combined with the traditional **CHOP** treatment as **CHOP-R**, but the literature and my advisors at the Mayo clinic suggested that the **H** and **O** agents were unnecessarily harsh and that the combination **CP-R** (cyclophosphamide, prednisone, and rituximab) should be effective enough with fewer side effects.

In January 2008, I began a series of six chemo sessions at three-week intervals, finishing in June. The treatments cut my IgM level in half and increased my hemoglobin from 10.8 to 13.0 g/dL. They also won me a prize with my local WM support group as the world's worst rituximab patient. The drug can cause the shakes, a red rash all over the body, and low blood

pressure leading to unconsciousness – all of which I experienced at one time or another. However, by slowing down the infusion rate, and by the careful use of steroids and opioids, we learned to manage the side effects and continued to use the drug.

This seems as good a time as any to comment on active membership in a local support group. I belong to two – one for lymphoma of all types, and the other for WM, my own particular form. The larger group (lymphoma) has formal meetings with invited speakers as well as a general roundtable discussion forum, while the smaller (WM) group is less formal, with fewer speakers and more emphasis on the psychological support available from a group familiar with your particular problems. It has become a closely-linked community – both a big advantage as well as a bit stressful, given the rate at which members die off (an average of one a year or so for a group of around ten patients). For me, active participation remains a vital tool in dealing with WM.

By June 2010, my hemoglobin had fallen back down to 10.1 g/dL and my IgM had doubled, so a second round of chemotherapy was required. My oncologist had experienced success with cladribine plus rituximab on several other patients, so we tried that combination in June and July of 2010. The treatment was not as successful as the **CP-R** had been, and the literature was beginning to arouse concerns about cladribine causing secondary cancers and degrading the bone marrow's stem cells. As a result, we stopped after only two treatments, and spent the next six months seeking another, more effective, less toxic treatment.

At this point, I spent quite a bit of time following up on a paper published by the Mayo Clinic saying that autologous hematopoietic stem cell transplants (transplants of blood-cell-forming stem cells harvested from one's own bone marrow) should be used more in the treatment of WM. I learned that in order to achieve a successful stem cell harvest, it is necessary to first achieve a strong remission from the disease. It is also necessary to select a

treatment that is not too hard on the stem cells themselves. Over time, it had been found that **CHOP-R** was about the least harsh treatment, and as effective as any. So that was what we selected.

From June to November 2011, monthly **CHOP-R** treatments were planned, although severe side effects and hemoglobin plummeting to 5.0 g/dL caused pauses and delays. On the other hand, persistence paid off – the treatments took my hemoglobin back up to 15.2, reduced my IgM to normal levels, and gave me a four-year remission of quite good health.

The remission looked so strong that the Stem Cell Transplant Unit at the Ottawa General Hospital tried to harvest my stem cells in early 2012, but failed to obtain a useful quantity of cells despite the use of a relatively new wonder drug (Mozibil) to reduce the stem cells' tendency to concentrate in the bone marrow. By September 2012, things were going so well that I persuaded them to try again. This second attempt proved to be successful.

The stem cell harvesting process is very interesting. You are pretreated overnight with Mozibil before each harvesting sessions. I found the procedure profoundly disturbing, as it caused me to awaken in the middle of the night with heavily depressed thoughts for three or four nights. But, fortunately, I found myself able to deduce their origin and simply let them pass. Then, in the hospital, for the actual collection of the cells, blood is pumped out of one arm, passed through a centrifuge, and pumped back into your other arm. There is a slit which allows a nurse to see the blood gradient – from the dark red cells at the bottom (the dense end) to light yellow plasma at the top. A pair of nurses shared in managing the process for eight hours or so, guiding a very small siphon to suck up material from the margin between red and yellow, where the stem cells are found. Canadian Blood Services assesses the resulting harvest, freezes the cells, and determines whether more Mozibil and a second day are required to obtain sufficient cells for a successful transplant. I produced only 75% of

the minimum on day one, and the supervising physicians feared that a second day might prove insufficiently productive. Fortunately, day-two yielded enough to just meet the minimum standard without completely exhausting interesting topics of conversation for me and the nurses.

We celebrated by going on a three-week wilderness canoe trip later that week.

The above activities highlight the importance of key players on the team that provides vital support through all the tough sledding of multiple chemo sessions, raging infections, high doses of steroids, and other problems that make a patient such a joy to be around. When I said "**We** celebrated . . ." I was, of course, including my wife, Aileen. I hate to think of trying to get through all my treatments without a loving, caring partner. Other key players are the nursing staff of your local cancer center, whose care will be a regular and critical part of your life. I have already mentioned my great fortune in finding a wonderful, almost collegial, hematologist/oncologist and the psychological reinforcement provided by local disease-specific support groups. The on-line advice provided by an international support group's chat line is also extremely useful in learning of other patients' experiences before going through them yourself. Finally, the acceptance and interest expressed by close friends does help cope with many of the tough times.

By July 2015, my hemoglobin levels had fallen back down to about 10.0 g/dL, so it was time for further treatment. In order to achieve a successful stem cell transplant, it would be necessary to use chemotherapy to provide a relatively healthy starting point. So, the research of options for my next treatment began in earnest.

Fortunately, a new option had just presented itself. During the four years of my remission, a team at Dana-Farber Cancer Institute had discovered a single genetic mutation present in 95% of WM patients. It prevents production of a single protein (BTK) that plays a key role in a known biochemical pathway that usually limits the lifespan of the normal B cells

produced by the bone marrow. Those mutated cells do not die off as they should, but accumulate as cancer cells. A new drug, ibrutinib, while extremely expensive, seemed to treat this specific problem and was therefore expected to be more effective and less toxic than other chemo agents.

Careful research, an application to an Ontario specialty drug program, and a supplemental program run by the drug company enabled me to obtain ibrutinib. There had also been a development in CD20-specific antibodies: my old friend rituximab's side effects were largely due to the fact that 35% of the protein came from Chinese hamster cells used in its manufacture. Ofatumumab, a purely human-protein-based CD20-specific antibody, had just been developed and exhibited far fewer side-effects, so we switched to using it. This new chemotherapy option was administered in six monthly sessions from September 2015 to March 2016.

At this point I ran into a problem. The chemo had prepared me for my stem cell transplant, and the Mayo Clinic advice continued to favor it. But Dana-Farber Cancer Institute advised that continuous use of ibrutinib and other new drugs should offer less risk and better results than the transplant. Senior staff of the Bone Marrow Transplant Unit discussed the choice with Aileen and me, but left the final choice to us.

The choice of regular use of ibrutinib for the rest of my life, with the literature beginning to show that a resistance could develop, was much less appealing than the somewhat riskier stem cell transplant therapy, which should offer about a four-year remission on average. So we elected to try the latter.

The transplant process began in April 2016. It was, to say the least, an "interesting" experience. After three days of intensive chemotherapy and one day of radiation therapy, your bone marrow has been entirely destroyed. You then see a small handcart, like an ice cream cart, wheeled to your bedside by Canadian Blood Services and a very small bag of pinkish

liquid attached to your IV. This bag contains your stem cells, thawed out after four years of storage at minus 196° Celsius. There is no "Plan B". Your life is in that bag! If anything has gone wrong in those cells' processing, storage, transport, or thawing, it is game over, lights out. As I said, an interesting and unforgettable experience!

The recovery process was performed as an outpatient exercise. It involved spells of hospitalization as required to treat various infections, great care taken on personal hygiene, and avoidance of social contact for about six months. At that point, all childhood vaccinations have to be performed on your newly-born immune system. Each of the four sets of shots gave me pneumonia, so I spent more time in hospital in the second six months than the first. An annoying cough persisted for four months, but has just now (July 2017) been killed off by antibiotics, antifungals and antivirals during my last stay in hospital.

It turns out that my stem cells have suffered from my many bouts of chemotherapy and have acquired a moderate level of myelodysplastic syndrome (MDS). This means that they are no longer capable of producing normal amounts of healthy blood cells, but so far they seem to be able to support a carefully restricted lifestyle. By avoiding obviously disease-risking situations and working hard to keep as fit as possible, I have every confidence that I can carry on for several years before undergoing any further treatment. I had been making a habit of outliving WM's survival curve (only 25% of patients diagnosed when I was have survived to this point), so I regard my intermediate level of MDS's 4-year average survival curve as just another challenge to be overcome.

It seems worth concluding this story by revisiting the concept of cancer as a hobby. As you have seen, it has dominated my life for fifteen years at this point, and it has provided me with lots of interesting work keeping up-to-date with treatments for WM and now MDS. It also has led me to a high level of support group participation and to occasional international travel to

WM conferences, to Dana-Farber and to the Mayo Clinic. I have found it extremely important to restrict the bouts of research and consultation to key decision points, putting the whole thing out of mind most of the time. As with a hobby, WM is a fascinating subject if kept within boundaries, but could easily become an obsession. Close friends take an interest in how I am doing, and it is important to have a brief summary at the ready, but no-one wants the subject to dominate conversation. On the whole, it is a hobby I can live with.

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