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Non-Hodgkin's Lymphoma

Non-Hodgkin's Lymphoma is currently the fifth most common cancer in the United States. For reasons as yet undetermined by scientists, it has become increasingly more common over the last several decades. Fortunately, the future of Non-Hodgkin's Lymphoma looks to be promising, as research for new treatments has proved fruitful in the last decade.

Lymphoma refers to cancer of the lymphatic system, and is broken up into two types: Hodgkin's and Non-Hodgkin's. Hodgkin's disease is identified by "specific cells - Reed-Sternberg cells - that are not found in any other cancerous lymphomas or cancers" (NHL[1])Both of these diseases involve a mutation among B lymphocytes – a type of white blood cell - which causes them to divide much more rapidly than normal cells. Unfortunately, it is not currently known what causes this mutation, and much research is being done to discern the cause of this disease, particularly because its victims are growing rapidly in numbers.

Because Non-Hodgkin's Lymphoma (NHL) affects the entire immune system, not simply one immobile organ, it is constantly in motion throughout the body. In comparison to Hodgkin's disease, NHL "is much less predictable … and has a far greater predilection to disseminate to extranodal sites" ("Adult NHL"). Tumors can thus form near lymph nodes, as would be expected, or more obscure parts of the body that are used as gateways between two areas through which lymphocytes must travel (Patlak). As a result of this, there are many different ways that it can manifest itself depending on where

the tumor forms. The most identifiable symptom is the swelling of lymph nodes, but when other organs are infected, however, the symptoms often resemble those of many other common ailments. For example, "NHL in the digestive tract can cause nausea, vomiting, or abdominal pain; in the chest, shortness of breath or cough may develop. If the brain is involved, patients may have headaches, vision changes, or seizures. If the bone marrow is affected, lymphoma cells may crowd out red blood cell precursors, causing anemia" (Patlak). As a result of such varied and fairly common symptoms, the only way to confidently diagnose the disease is through a biopsy. In this procedure, tissues from the area suspected to be cancerous are removed and carefully examined. Once the cells are identified as NHL cells, they must be further inspected to conclude the specific type of NHL.

NHL is made up of over a dozen different types of cancers, which are classified by appearance, possible treatments, and disease progression at the time of diagnosis. The most general standard for classification is intensity: low-, intermediate-, and high-grade, although the assigned degree does not necessarily correlate with ease of treatment. Low-grade lymphomas, also known as indolent NHL, are slow-growing tumors and present no sense of urgency in treatment. They are generally responsive to chemotherapy initially, but have a high rate of recurrence. "Over time, low-grade NHLs tend to become more aggressive and less responsive to therapy," (Patlak) so that these indolent cancers actually end up more lethal than the aggressive forms. Intermediate- and high-grade lymphomas necessitate more urgent and potent treatment, but are often successfully cured by standard chemotherapy and radiation.

The term "chemotherapy" simply refers to the general mixture of drugs given to patients, and these drugs can be combined in several different ways in order to create the most appropriate treatment regimen for each patient. There are several different types of chemotherapy drugs, which include the following categories: topoisomerase inhibitors, tubulin binding agents, alkylating agents, antimetabolites, and immune suppressants ("Treating NHL"). In various ways, all of these drugs work by interfering with the replication of the DNA in the cancerous white blood cells, which stops tumor formation by inhibiting cell division. Chemotherapy drugs are focused on rapidly-dividing cells. As a result, while cancer tissues are directly affected by these drugs, they also affect healthy rapidly-dividing cells, which could include "the bone marrow, the lining of the mouth and intestines, and the hair follicles" ("Overview"). This accounts for the long list of detrimental side effects to this procedure, ranging from hair loss to intense nausea and vomiting, and as a result, any chemotherapy regimen also includes several drugs intended to counteract the side effects of the primary drugs. Chemotherapy is given in 3-4 week cycles generally totaling roughly a 6-month treatment period.

Another common treatment, often used in conjunction with chemotherapy, is radiation. Radiation uses x-rays to stop the growth of cancer cells in the body. It does this by "changing the structure of molecules that make up the cell's DNA" ("Treating NHL") by removing electrons from atoms in the molecule, causing them to bind to one another in different ways. Side effects are generally minimal because radiation can be much more targeted than chemotherapy. Other tissues are hit with the radiation, but those cells are much less susceptible to the x-rays than cancer cells. Because cancer cells are constantly dividing, they are much more likely than normal cells to have their DNA

uncoiled and separated, the way it is during DNA replication, and it is only during this phase that the radiation can be effective ("Treating NHL").

In patients with particularly aggressive cancer who have had several recurrences, it is often necessary to use a much higher dose of chemotherapy. When this is the case, it is generally done with either a bone marrow or a peripheral blood stem cell transplant. In a bone marrow transplant, "marrow is taken from the bones before treatment. The marrow is then frozen and the patient is given high-dose chemotherapy with or without radiation therapy to treat the cancer" ("NHL"). The original marrow is then returned to the patient to replace the bone marrow that was destroyed. This procedure can be either allogenic (where the marrow that is put back into the patient is from a donor), or autologous (where the patient's own bone marrow is used, in which case the removed bone marrow is generally treated to kill any existing cancer cells within it). ("NHL") A peripheral blood stem cell transplant is just a slight variation on this procedure. Instead of bone marrow, just the patient's blood is withdrawn, and the stem cells within the blood – cells which can differentiate into any type of blood cell when required - are separated out. The rest of the procedure is the same, replacing the stem cells back into the patient to replenish the supply of blood cells that were killed in the intense chemotherapy. There are pros and cons to both versions of the procedure, but "if donor marrow is used, the attack of incoming alien white blood cells against your tissues, called a graft-versus-host reaction, also confers a graft-versus-lymphoma effect that may overcome any residual cancer cells" ("Treating NHL"). This infliction, generally an undesirable and somewhat dangerous disease that typically results in the failure of transplants, is actually a benefit to allogenic bone marrow transplants for NHL patients.

In the last 7 or 8 years a new type of treatment has become widespread and has had enormous success. In 1997 Genentech discovered a monoclonal antibody called rituximab, or Rituxan commercially, which is increasingly becoming a staple in the treatment repertoire. The basic idea behind monoclonal antibodies (mAbs) is that they bind to specific target cells and then notify the immune system of the presence of cancer cells. Each mAb has one specific target cell, or one specific antigen that it can bind to, so each one can only work for one very specific type of cancer. Rituximab is "directed against the CD20 antigen found on the surface of normal and malignant B cells" (Leget), where it induce the B cells to lyse. "Greater than 90% of B-cell NHLs express the CD20 antigen," and unlike radiation it is not dependent upon cell cycle to be effective ("Product Summary").

The specificity of monoclonal antibodies is one of the reasons they are so much easier on the patient in regards to side effects. Because they specifically bind to the B cells, only those cells are attacked by it, as opposed to every rapidly-dividing cell in the case of chemotherapy. MAb treatment is much more targeted only at the cancerous cells. In clinical trials, "the mAb demonstrated tolerable side effects, primarily limited to fevers and chills associated with the first infusion," (Leget) a vast difference from the pain of chemotherapy.

Rituximab showed incredible potential from the very start of its clinical trials. When used for four weeks in patients with low-grade or follicular lymphoma, 46% of the patients responded well to the drug. Rituximab was then combined with chemotherapy, and either a partial or complete remission was seen in all patients. (Ohnishi). This is

where rituximab seems to have found its place in NHL treatment. In combination with either chemotherapy or radiation it has worked wonders for many patients. With chemotherapy, the pairing of the two treatments has been incredibly successful because the "chemotherapy can be more effective when the cells are weakened by the mAb" (NHL[2]). When combined with radiation, "the mAbs contain a radioactive substance such as radioactive iodine that targets and destroys the cancer cells" (NHL[2]). The tumor is actually submitted to a dose of radiation from inside the body, and surrounding tissues are not at all affected by that radiation.

Monoclonal antibodies are currently being researched for many other types of cancer. Because of the success seen with NHL there is great hope that they can do wonderful things for other diseases as well. The truly amazing thing for many patients is the lack of side effects seen with them. In those patients for whom rituximab alone has been enough to incur remission, it is an incredible relief. Because it is most often used in patients who have experienced significant recurrence, undergoing treatment that allows you to go on with your daily life is an unimaginable blessing. And for those patients who do not have that luxury, but who must use it in combination with chemotherapy, it is often one of their last remaining options and has been successful in many cases. These therapies should continue to be researched extensively to find ways to make it even more effective for NHL patients, and for ways to apply this therapy to other diseases as well.

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