

Emerging Treatments for Hodgkin's Lymphoma & The Next Generation of Patients

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Table of Contents

Acknowledgements	3
Abstract	3
Introduction	4
Classical Hodgkin's Lymphoma	5
Nodular Lymphocyte Predominant Hodgkin's Lymphoma	6
Staging System & Prognostic Factors	7
Methodology	10
Results	11
Early-stage CHL Treatments	12
Advanced-stage CHL Treatments	15
NLPHL Treatments	17
Discussion	18
Preventing Adverse Side Effects	18
Controversies	20
Prevailing Misunderstandings	21
Conclusion	22
Methodology Recommendations	23
References	25
Appendix	28
I: CancerCare Conference Script	28
II: Lymphatic System Diagrams	33

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Abstract

Despite overall survival rates of in the high 80s and 90s, current treatments for Hodgkin's Lymphoma are not yet optimized (Ansell, 2012). High incidence of relapse, secondary malignancies, and long-term toxicity threatens survivors of this disease, especially in the young population. In this study, an analysis of current and emerging treatments for various subtypes of Hodgkin's Lymphoma was conducted, including potential side effects and controversies among health care professionals regarding standard of care. The role of clinical trials for prospective treatment advancements was discussed and recommendations concerning the screening and management of survivors were developed. The results in this paper were compiled based on a large review of the current literature and public conferences with experts. This paper summarizes the past, present and future treatments of Hodgkin's Lymphoma and potential risks that patients face as a result. In order to optimize the treatment of this disease, emerging therapies should aim not only to eliminate cancer cells and tumors, but also to reduce risks of future complications (Xing, 2013).

Introduction

With some of the most successful treatments in all of modern oncology, Hodgkin's Lymphoma (HL) is considered to be a "curable" cancer (Kadin, 2010). Every year, 9,000 people in the United States and 59,000 people worldwide are diagnosed with this disease (Marri, 2013). The affected patients are distributed between two main population groups: children, teens, and young adults in their 20s or adults over the age of 55. Although more than 80% of these newly diagnosed patients under the age of 60 will survive HL, current treatments contain potential severe side effects that may not present themselves for years or even decades after treatment (Ansell, 2012). Therapy advancements are currently being investigated to solve these life-threatening issues (Sweetenham, 2010). Over the past decade, researchers have discovered new potential targets for treatment, which are currently being tested through clinical trials. However, without a clear understanding of the biochemistry of this disease and how it behaves within body, none of these discoveries or emerging treatments for HL would have been possible (Sweetenham, 2010).

In general, lymphomas are cancers of the lymphatic system; a network of small vessels and lymph nodes containing cells called lymphocytes, which are essential in recognizing and fighting infections in parallel with the body's immune system (O'Connor, 2013). According to Dr. Steven Ansell, Professor of Medicine at Mayo Clinic, when lymphocytes are mistakenly transformed, they become "much more aggressive in their growth pattern and much more resistant to dying off." As a result, B-lymphocytes, those that produce antibodies, and T-lymphocytes, those that directly fight infection, do not perform properly and become cancerous; this is called lymphoma (Ansell, 2013). A study by Marafioti et al. (2000), specifically proved that the clonal cells of Hodgkin's Lymphoma originate from defects in transcription regulation and gene rearrangement of germinal center B-cells. Therefore, T-cell lymphomas are not characteristic of HL and will not be discussed in this study (Ansell, 2013). The transformed B-cells that characterize HL vary between the two major sub-types of HL: Classical Hodgkin's Lymphoma (CHL) and Nodular Lymphocyte-Predominant Hodgkin's Lymphoma (NLPHL) (Marafioti, 2000).

Classical Hodgkin's Lymphoma

According to World Health Organization, CHL is the most common type of HL and can be further divided into 4 sub-types: nodular sclerosis, mixed cellularity, lymphocyte depletion, and lymphocyte-rich HL (Swerdlow, 2008). In each of these sub-types, the presence of small, mono-nucleated Hodgkin's (H) cells and large, bi-nucleated or multi-nucleated Reed-Sternberg (RS) cells is pathologically consistent (Iyer, 2013). Interspersed between a background of reactive inflammatory cells, including lymphocytes, plasma cells, and other white blood cells, the neoplastic H and RS cells (also referred to as HRS cells) are actually in the minority, contributing to only 1-2% of the total cell count (Marri, 2013). As a result, large sample biopsies should be done in order to successfully view and identify HRS cells under a microscope (Ansell, 2013). RS cells specifically are large, 30-60 μm , with a bi-lobed, vesicular nucleus that is surrounded by what appears to be a clear halo (See Figure 1:A). H cells are similar but smaller, so they are more difficult to identify and are not as characteristic to cases of CHL (Abassi, 2012). Another important feature of RS cells is that their immunophenotype is regular, meaning that the same antigens are always expressed on the cell's surface. These antigens, or proteins, in RS cells are known as CD15+ and CD30+ (Iyer, 2013). Using a variety of current biological techniques, these antigens may be tagged to better highlight their location and therefore, the relative location of the RS cell itself (see Figure 1:B). With this information, the presence of HRS cells in a tumor can be used to make a CHL diagnosis (Ansell, 2013).

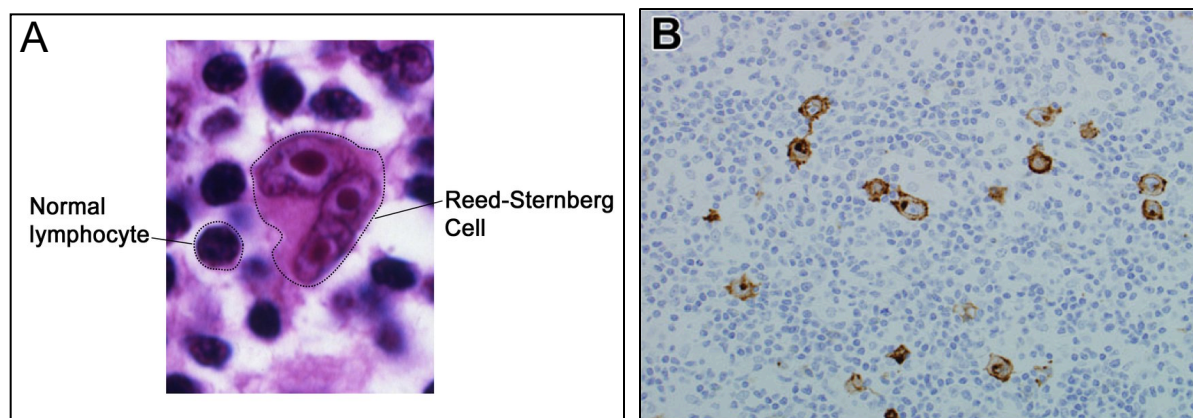


Figure 1: Immunohistochemistry of Hodgkin's Lymphoma. **A:** H&E staining of Reed-Sternberg cell and normal lymphocyte cell. Source: National Cancer Institute AV# CDR576466 **B:** CD30 expression in classical Hodgkin lymphoma highlighting the Reed-Sternberg cells. Source: Andrew Feldman, MD via (Ansell, 2012)

Along with HRS cell histochemistry and morphology, CHL and its sub-types can be further classified according to a variety of clinical features including the following: the affected age group (e.g. children and young adults or adults above the age of 55); the predominant gender of those affected; B symptoms present such as fever, night sweats, and weight loss; nodularity or the development of a lump from highly dense tissue; and the components of background reactive inflammatory cells (e.g. T-cells, B-cells, plasma cells, histocytes, eosinophils, or other white blood cells) (see Table 1) (Iyer, 2013). Proper identification of these clinical and histochemical features as well as potential variants of HRS cells, such as smaller lacunar cells in Nodular Sclerosis HL, are all important in order to successfully diagnose a patient with CHL (Ansell, 2013).

Type	Age	Predominant Sex	B symptoms	Nodularity	Background cells	Type of RS cell	Immuno-phenotype
Nodular sclerosis CHL	Children & adults	Females & males (equal)	Present	Present	T-cells, eosinophils, plasma cells	Lacunar cells	CD15+, CD30+
Mixed cellularity CHL	Children	Male	Present	Absent	T-cells, eosinophils, plasma cells	Classical	CD15+, CD30+
Lymphocyte depletion CHL	Adults	Male	Present	Absent	T-cells, histocytes	Classical & bizarre	CD15+, CD30+
Lymphocyte rich CHL	Children & adults	Male	Absent	Present	B-cells of mantle type	Classical	CD15+, CD30+
NLPHL	Adults 30-50	Male	Absent	Present	B-cells, T-cells collar	Popcorn cells	CD20+, CD15-, CD30-

Table 1: Clinical presentation and histochemical features of Hodgkin's Lymphoma. Source: (Iyer, 2013)

Nodular Lymphocyte Predominant Hodgkin's Lymphoma

Affecting only 5% of all cases, NLPHL is a fairly rare variant of Hodgkin's Lymphoma in western countries (Xing, 2013). Not only is the incidence of NLPHL significantly lower from that of CHL, but also the histochemical and clinical features differ substantially (see Table 1). The transformed B-cells of NLPHL are atypical from the classical HRS cells of CHL and are called Lymphocytic and Histiocytic (L&H) cells or popcorn cells, due to their lobulated popcorn-like morphology. According to the World Health Organization, these popcorn cells must present with at least a partial nodular pattern to be considered NLPHL (Novagá, 2013). In contrast to the CD15+ and CD30+ antigens of RS cells in CHL, popcorn cells express CD20+, CD30-, and CD15-. As a result, immunophenotyping by flow cytometry should be done to verify the antigen

expressed and to ensure that an accurate diagnosis and treatment plan is determined (Iyer, 2013). Without proper immunophenotyping, NLPHL can easily be mistaken with lymphocyte-rich CHL (see Table 1), a sub-type of CHL that was only recently added to the WHO's classification of Hodgkin's Lymphoma (Swerdlow, 2008). In a 2000 study by the European Task Force on Lymphoma (ETFL), 30% of the original 338 NLPHL diagnosed cases were re-classified as lymphocyte-rich CHL according to distinct morphological and immunophenotypic criteria. This study questions the accuracy of previous NLPHL cases and emphasizes the importance of a proper initial diagnosis and review by expert haematopathologists that could effect the treatment given (Xing, 2013).

Staging System & Prognostic Factors

According to Dr. Ansell, "once the initial diagnosis regarding the type of HL is made, the next most critical step is to determine the staging of the disease." He points out that disease-staging measures clarify the level of advancement of a disease and are therefore vital in the determination of future management and treatments (Ansell, 2013).

Stage	Description
I	Single lymph node region (e.g. cervical, axillary, inguinal, mediastinal) or lymphoid structure
II	Two or more lymph node regions of lymph node structures on the same side of the diaphragm
III	Lymph node regions or lymph node structures on both sides of the diaphragm III-1: With or without involvement of the spleen/splenic hilar, celiac, or portal nodes III-2: With involvement of the Para aortic, iliac, inguinal, mesenteric nodes
IV	Diffuse or disseminated involvement of one or more extra nodal organs or tissue with or without associated lymph node involvement
A	No B (systemic) symptoms
B	B (systemic) symptoms: Fever > 100.4°F, night sweats, unexplained weight loss > 10% over 6 months
E	Involvement of single contiguous extra nodal site or proximal to known nodal site
X	Bulky disease present. Mediastinal mass with a maximum width > 1/3 of the internal transverse thoracic diameter at T5/6 level or >10cm maximum dimension of a nodal mass
CS	Clinical Stage
PS	Pathological Stage

Table 2: Ann Arbor staging system of Hodgkin's Lymphoma with modifications. Source: (Marri, 2013)

Patients can be staged clinically, by direct observation, or pathologically, by surgically removing tissue samples (Mauch, 2013). In addition, computerized tomography (CT) imaging, chest x-rays, fluorodeoxyglucose positive emission tomography (FDG-PET) scans, and occasionally bone marrow testing for more advanced patients are all important tools used for HL staging (Xing, 2013). Recent

studies have shown that even though FDG-PET scans have an increased number of false positives, they are, in general, more diagnostically accurate than CT scans. Therefore, for the most accurate diagnosis, FDG-PET and CT scans should both be performed collectively (Marri, 2013). The criteria for staging can be seen in Table 2.

In order to fully understand and properly use this staging system, one should be familiar with the anatomy and physiology of the lymphatic system including the locations

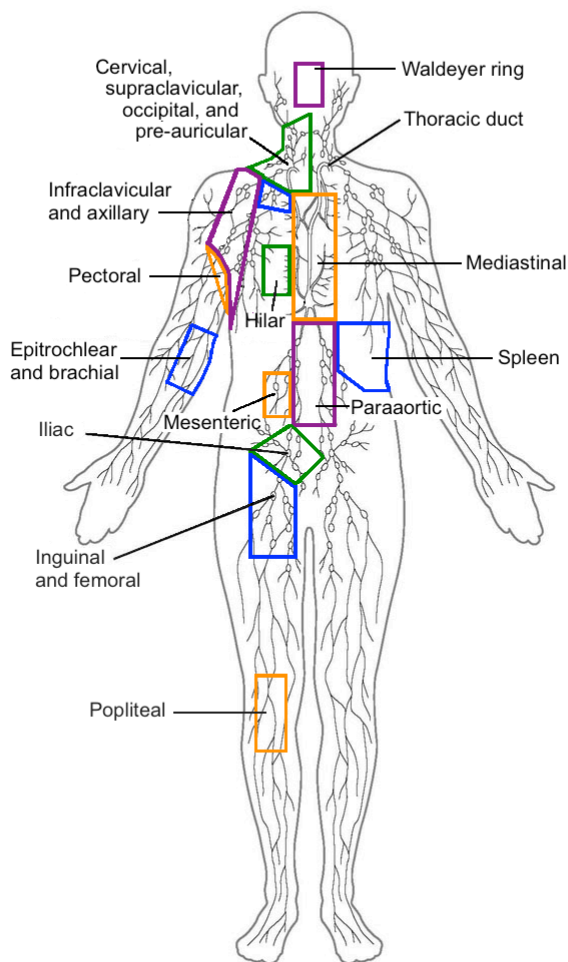


Figure 2: Lymphatic system anatomy and lymph regions. Source: National Cancer Institute & Webscape (See Appendix)

of lymph nodes within the body. Firstly, it is important to know that the average person has roughly 600-700 lymph nodes, which are grouped into regions for ease of specification (see Figure 2) (Buggida, 2013). When making a diagnosis of HL, the location of these regions in relation to the diaphragm and the number of involved regions are taken into account (Marri, 2013). HL and other lymphomas are most commonly found in the neck and chest (Buggida, 2013). Secondly, it is important to know that the lymphatic system is not just comprised of lymph nodes, lymph vessels, and lymphocytes. The spleen, the thymus, and the tonsils are also major parts of the lymphatic system due to their abilities to process, store, and recycle lymphocytes (Buggida, 2013). Any involvement in these extra nodal regions immediately progresses HL to stages III

and IV; these are known as the advanced stages. The early stages (I & II), also known as the limited stages, involve only lymph nodes on one side of the diaphragm (Marri, 2013). Lastly, it is important to know that each stage (I-IV) can be divided into sub-categories. A and B represent either the absence or the presence of B (systemic)

symptoms such as unintentional weight loss, drenching night sweats, and fevers over 100°F, respectively (Hoppe, 2013). According to Dr. Ansell, severe itching, though not a constitutional symptom, is also often present in the 1/3 of HL patients that present with B symptoms (Ansell, 2013).

Once the initial stage of HL is diagnosed, prognostic factors are then reviewed to predict the behavior of the development of the disease. For patients with early-stage (I-II) disease, the prognosis can be either favorable or unfavorable and is based on definitions set by the European Organization for Research and Treatment of Cancer (EORTC), the German Hodgkin Study Group (GHSG), and the National Cancer Institute of Canada (NCIC) (Marri, 2013). Unfavorable prognostic features include; large mediastinal mass or bulk; an elevated erythrocyte (red blood cell) sedimentation rate (ESR) due to infection; greater than 3 involved sites of disease; the presence of extra-nodal sites, especially in the spleen; and advanced age (See Table 3) (Hoppe, 2011).

Early Stage Disease Unfavorable prognostic factors		Advanced Disease Adverse prognostic factors
GHSG definitions	EORTC definitions	Age ≥ 45 years
Large mediastinal mass	Large mediastinal mass	Stage IV disease
Elevated ESR	Elevated ESR	Male gender
Involved sites ≥ 4	Involved sites ≥ 3	WBC ≥ 15,000 cells/μL
Age ≥ 50 years	Extra-nodal sites involved	Lymphocytes < 600 cells/μL
	Large spleen involvement	Albumin level < 4g/dL
		Hemoglobin level < 10.5g/dL

Table 3: Prognostic factors of early-stage and advanced-stage disease. Based on the German Hodgkin Study Group (GHSG) and the European Organization for Research and Treatment of Cancer (EORTC). Source: (Marri, 2013).

For patients with advanced (III-IV) disease, prognosis is based on a different system, called the International Prognostic Score (IPS), due to the fact that the traditional prognostic factors mentioned above are not always accurate for advanced predictive behavior (Marri, 2013). In this system, the presence of each adverse prognostic factor increases one's IPS by 1 and decreases one's survival rate by 7-8% per year (Hoppe, 2011). Patients with an IPS greater than 5 have a 42% chance of being free from progression after 5 years while patients with an IPS of 0 have an 84%

chance. The list of the 7 adverse prognostic factors for advanced disease in Table 3 is based on the International Prognostic Factor Project for advanced HL (Ansell, 2012).

HL patients are generally classified into one of 3 groups; early-stage favorable, early-stage unfavorable, or advanced disease. Depending on the designated group assigned and the major subtype of HL diagnosed, treatments for HL patients will vary greatly (Hoppe, 2011). The following research will analyze the current and emerging treatments used to treat HL, the long-term side effects of these treatments, and what could be done to better monitor and reduce patient risks.

Methodology

The majority of the research conducted for this paper is based on an extensive review of the current literature. The National Center for Biotechnology Information (NCBI), which is part of the U.S. National Library of Medicine was used to search for and organize articles through a personal account that was set up with them on their website, <http://www.ncbi.nlm.nih.gov>. Of the databases that they offered as search engines, PubMed and PubMed Central® were used.

Key words used for searches for the Introduction section include the following: “Hodgkin’s lymphoma”, “Hodgkin lymphoma”, “Hodgkin lymphoma overview”, “Hodgkin’s disease overview”, “classical Hodgkin’s lymphoma”, “classical Hodgkin’s lymphoma vs. n1ph1”, “reed Sternberg cells”, and “origin of reed Sternberg cell.”

Key words used for searches for the Results section include the following: “Hodgkin lymphoma treatment”, “early stage Hodgkin lymphoma treatment”, “hodgkin lymphoma chemotherapy options,” “abvd vs beacopp therapy”, “rituximab Hodgkin lymphoma”, “clinical trials structure” and “involved field radiation therapy scattering.”

Key words used for searches for support in the Discussion section include the following: “fear of clinical trials”, and “Hodgkin lymphoma side effects.”

Two filter systems were used in the search, “Sort by Recently Added” and “Sort by Relevance,” which resulted in varying articles for the same keywords. When an article of interest was unavailable for the general public to read, the Lehigh University Database Finder was used to access necessary subscriptions to the online journal. Additionally, <http://www.google.com> and <http://scholar.google.com> were used to find websites with basic information on Hodgkin lymphoma and other peer-reviewed articles.

In addition to the literature review, an online conference offered by CancerCare was used and transcribed. The recording for this conference, *Emerging Therapies in Hodgkin's and T-cell Lymphomas*, is open to the public and a partial script can be found in Appendix I at the end this paper. To further enhance this source, articles in the literature from the participating doctors were used as well. Obtaining personal interviews with practicing physicians in the United States and Switzerland was attempted through email, however no responses were received.

Figure 2 of the lymphatic system anatomy and lymph node regions was created by combining information from two distinct diagrams available online; one from Webscape and one from the National Cancer Institute (NCI) (See Appendix II). The paintbrush application for Mac was used to add all labels as well as the colored boxes representing each lymph node region.

Ethical considerations regarding proper citations were considered throughout the research process. Since all sources from the literature and the conference used are available to the public, human subject review and consent was not needed here.

Results

Before an investigation of the current and emerging treatments of HL can be conducted, it is valuable to understand that before a new cancer therapy can be approved for use, it must pass a variety of tests (O'Connor, 2013). The clinical, regulatory, institutional, and cultural approaches to these tests will vary by country, however the general purpose of developing new, safe, and successful treatments is consistent (Reekie, 2012). Regulations in the United States require that a drug must first survive several years of research in a laboratory setting as well as testing on animals. Only then can it be approved for human testing through clinical trials. Once approved, the cancer treatment passes through four phases; the first phase assesses the treatment's safety, the second phase assesses the treatment's efficacy, the third phase assesses the treatment's superiority over current therapies, and the fourth phase assesses the treatment's ability to be used on a large scale. With only 0.1% of emerging cancer treatments in the United States making it to Phase I of clinical trials, it is clear that only the most promising treatments are tested on human patients (Fin, 1999).

As mentioned earlier, the World Health Organization recognizes two major types of Hodgkin's Lymphoma, Classical Hodgkin's Lymphoma (CHL) and Nodular Lymphocyte-Predominant Hodgkin's Lymphoma (NLPHL) (Marafioti, 2000). It has been debated whether NLPHL should be treated differently from CHL, but the disease rarity and lack of survival statistics makes individual therapies difficult to standardize (Xing, 2013). The following is an overview of current therapies being prescribed and emerging therapies that may prove more effective. Side effects of these treatments are also mentioned.

Early-stage CHL Treatments

With overall survival rates for newly diagnosed HL patients in excess of 90%, this disease is almost curable thanks to decades of medical research (Sweetham, 2010). Generally today, combined modality therapy (CMT) is used to treat patients with early-stage CHL, meaning that they are treated with a combination of chemotherapy and radiation therapy (Ansell, 2013). Formerly, patients were treated solely with extended field radiation therapy (EFRT), which targeted both involved and surrounding lymph nodes to prevent further cell growth (Marri, 2013). However, high relapse rates and long-term complications have ceased the practice of this therapy (Hoppe, 2011). Some of these complications include thyroid disorders, impaired bone growth, infections, chronic fatigue, infertility, heart disease, and stroke. The side effects vary depending on where the radiation is concentrated and which radiosensitive tissues are impacted (URAC, 2008). Nowadays, involved-field radiation therapy (IFRT), which targets only the involved lymph nodes, is the standard radiation therapy given due to its decreased risks of side effects (Ansell, 2012). Though it is important to know that non-targeted tissues may still experience low-to-moderate doses of radiation and may therefore be at risk for late radiation effects (Chera, 2009).

In regards to chemotherapy, numerous combinations of drugs have been developed and the choice of these modalities depends on individual patient characteristics (Chabner, 2011). The former standardized regimen, MOPP (mechlorethamine, vincristine, prednisone, and procarbazine), was developed to treat patients whose disease progressed after radiation therapy (Ansell, 2012). Despite its effective results in treating CHL, a high number of patients became sterile and/or

developed secondary diseases, such as acute myeloid leukemia. As a result of these complications, new combinations of drugs were proposed (Sweetham, 2010). The ABVD regimen (doxorubicin [adriamycin], bleomycin, vinblastine, dacarbazine) was developed due to its excellent balance between efficacy and toxicity and it is still used today (Advani, 2011). A more aggressive regimen, BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone), is also available for more advanced patients (Marri, 2013). Though toxicity levels vary between treatments and the dosing of those treatments, it is important to know that each individual drug presents with its own long-term side effects. For example, decreased lymphocyte count leading to infection, chronic fatigue, osteoporosis, heart failure, and lung toxicity are potential complications of the regimens currently being used (URAC, 2008).

Depending on the favorability of a patient's prognostic factors (favorable vs. unfavorable), the dosage of the prescribed treatments will vary slightly (Ansell, 2013). Based on randomized trials conducted but the GHSG, patients with early-stage favorable CHL should receive a smaller dose of IFRT at 20Gy and a shorter duration of chemotherapy, generally 2 to 3 cycles. Meanwhile, patients with early-stage unfavorable CHL should receive a higher IFRT dose of 30Gy with 4 cycles of chemotherapy (Marri, 2013). Today, the standard chemotherapy regime is still a topic of debate and will depend on the country of treatment. For example, ABVD chemotherapy is considered the standard primary treatment in North America while elsewhere (e.g. Germany and Austria) BEACOPP is considered the standard primary treatment (Ansell, 2012).

This debate continues due to the varying efficacy and toxicity results of each therapy, which are continuously being studied (Sweetham, 2010). For example, BEACOPP therapy has shown to have significantly higher 5-year progression free survival rates and 5-year freedom from treatment failure rates compared to ABVD therapy (Marri, 2013). However, HL patients often relapse and require second treatment according to Dr. Connors. Therefore, in order to identify a superior treatment plan, one should also look to minimize the long-term side effects as well as freedom from secondary malignancies (Connors, 2012). The combination of higher toxicity levels and

higher survival rates for BEACOPP chemotherapy has made the use of this treatment controversial (Advani, 2013).

Radiation therapy for early-stage CHL patients has also been a topic of debate for several decades and chemotherapy-only approaches or reduced radiation therapies are currently being studied (Advani, 2011). According to Dr. Connors, radiation for 85% of early-stage HL patients is not necessary and as a result, many patients are being toxically over-exposed. However, he continues to point out that it is unreasonable to assume that simply decreasing the radiation will prevent any adverse effects (Connors, 2012). One study, submitted to the American Society of Hematology, treated patients with 6 cycles of AVG (doxorubicin, vinblastine, gemcitabine) chemotherapy alone, as compared to those additionally treated with radiation therapy. It was found, however, that these patients had a significant decrease in progression free survival. As a result and due to lack of additional evidence, IFRT continues to be considered a standard therapy in CHL treatment, though exceptions may apply. This clinical trial also tried to reduce lung toxicity side effects from bleomycin in traditional ABVD chemotherapy by removing it from the regimen. However, results were unproductive. Nonetheless, without clinical trials like this one, today's effective treatments may have never been and future emerging treatments may never be successfully implemented (Marri, 2013).

Some of the emerging therapies being developed for CHL are called targeted therapies because they are biologically designed to target the cancer cell's surface proteins, messaging pathways, or support structure that are necessary for survival (Ansell, 2013). For example, brentuximab vedotin targets and binds to the CD30+ antigens on the surface of HRS cells and as a result, delivers toxic chemicals to the cell. Other emerging drugs that initiate tumor cell apoptosis include; panbinostat, which inhibits histone deacetylase enzymes in the DNA; lenalidomide, whose mechanism of action is unclear but probably includes T-cell activation and blood cell destruction or antiangiogenesis (Sweetenham, 2010); and everolimus, which inhibits the mammalian target of rapamycin (mTOR) regulatory protein (See Table 4) (Ansell, 2012). The safety and efficacy of these drugs as well as many others are still being investigated through clinical trials (Marri, 2013).

Drug	Class of drug	Overall Response Rate (%)
Brentuximab vedotin	Antibody-drug conjugate (anti-CD30)	75
Panobinostat	Histone deacetylase inhibitor	27
Lenalidomide	Immunomodulatory agent	19
Everolimus	Mammalian target of rapamycin inhibitor	47

Table 4: Response Rates of Emerging Treatments for Relapsed and Refractory HL Patients.
Source: (Ansell, 2012)

Advanced-stage CHL Treatments

For over 30 years, medical advancements in the treatment of advanced-stage HL patients have increased tremendously (Advani, 2011) with a current overall survival rate greater than 85% despite the disease's aggressive nature (Sweetham, 2010). Patients with advanced-stage CHL are generally treated with high doses (usually 4-6 cycles) of chemotherapy and no radiation therapy (Ansell, 2012). In North America, ABVD chemotherapy is most typically given, though patients with unfavorable prognostic factors may be considered for other dose-intense regimens (Marri, 2013). One of these regimens, the Standard V regimen, combines the less toxic active agents of the ABVD and MOPP chemotherapy in an attempt to decrease long-term complications. It is also a combined modality therapy and therefore includes radiation therapy. In general, studies have not shown this regimen to be significantly better than ABVD in terms of overall survival rates (Advani, 2011). However, patients with lung problems should consider being treated with Standard V due to increased pulmonary toxicities associated with ABVD chemotherapy (Ansell, 2012).

Another dose-intense regime for advanced-stage CHL patients is BEACOPP. However, as previously seen in early-stage CHL, controversies regarding efficacy and toxicity continue in the advanced-stage, potentially even more so (Ansell, 2012). The GHSG and EORTC insist that escalated BEACOPP should be the standard therapy for advanced-stage CHL, though other organizations and medical professionals are not so convinced (Chustecka, 2013). Many doctors believe that as an aggressive regimen, BEACOPP should only be used to treat the most aggressive forms of HL (i.e. those with IPS > 4 or relapsed & refractory patients) (Marri, 2013). As stated by Dr. Dan Longo from Harvard Medical School in Boston, using BEACOPP as standard primary treatment is "over-treating the majority of patients" who could otherwise be treated less

toxically and just as successfully with ABVD therapy. To comprise for this, some doctors have proposed the approach of using ABVD for the first two cycles of chemotherapy followed by an FDG-PET scan to assess whether more aggressive, BEACOPP treatment is necessary. Additionally, a combination of the two therapies, ABV-COPP, may be administered as well (Chustecka, 2013).

Despite these proposals, many doctors, may still be hesitant - but why? The answer may be due to salvage therapy, or the second-line of treatment used for relapsed and refractory patients. With 20-30% of HL patients either failing their primary treatments or having their HL return, effective salvage therapy is especially important (Ansell, 2012). Dr. Longo points out that unlike other cancers, HL has very promising and successful second-line treatments (Chustecka, 2013). Generally, this treatment is high-dose chemotherapy and an autologous stem cell transplant (HDCT/ASCT) (Xing, 2013), in which one's own stem cells are used to rescue and replace the healthy cells that are damaged from the high doses of chemotherapy (Ansell, 2013). However, if a patient previously received BEACOPP chemotherapy as primary treatment, he or she is often illegible or benefit less from HDCT/ASCT. This was proven in a recent clinical trial from the Oncology Institute of Southern Switzerland, which found that patients previously treated with ABVD have a 76% 5-year progression free survival rate after salvage therapy, while that of patients previously treated with BEACOPP is only 42%. Nonetheless, the overall survival rate with BEACOPP is still greater. For this and many other reasons, the controversy between ABVD and BEACOPP chemotherapy for advanced-stage CHL patients continues and clinical trials are being done to develop more definite answers (Chustecka, 2013).

Even though 4-6 cycles of ABVD chemotherapy is the standard treatment for advanced-stage CHL in North America, it is important to keep in mind that other options are available and should not be over-looked (Ansell, 2012). Treatment options may vary from standard care according to individual patient characteristics and needs (Chabner, 2011). Additionally, emerging treatments for advanced-stage CHL, which are similar to those of early-stage CHL, may be added to the current regimens (Sweetenham, 2010).

NLPHL Treatments

NLPHL is a rare form of HL that accounts for only 5% of all HL cases (Novogá, 2011). The disease is characterized by its indolent course and as a result 75-80% of the diagnosed patients present with early-stage disease (Xing, 2013). Due to the rarity of this disease, especially among advanced patients who only make up only 20-25% of all NLPHL patients, optimal treatments and survival statistics are quite unknown (Xing, 2013) and in order to define more optimal therapies for the future, clinical trials are currently being done (Ansell, 2012). Standard therapies for NLPHL today are equivalent to those mentioned previously for CHL, with the exception of NLPHL stage I (Novogá, 2008). Patients with stage I are generally treated in 1 of 2 ways. The first form of treatment, an IFRT dose of 30Gy to the involved lymph node, is the most traditional and statistically proven treatment (Novogá, 2008). In contrast to early-stage CHL, chemotherapy is not included here because in a study by the Australasian Radiation Oncology Lymphoma Group, the addition of chemotherapy to radiotherapy did not improve progression free or overall survival rate for stage I NLPHL patients. The additional chemotherapy could rather negatively increase the patient's risk of side effects. Furthermore, of those treated with chemotherapy alone, 86% developed early-stage progression (Hoppe, 2011). Even so, it is important to keep in mind that low dose radiation treatment alone is not exempt from long-term complications and other treatment options should be considered (Xing, 2013).

Another way to treat early stage NLPHL is by performing a lymphadenectomy, or surgically removing the involved lymph node(s), followed by a "watch and wait" protocol to see if the disease progresses. This option, though it is less toxic, is generally restricted to patients who are trying to avoid adverse side effects, such as children. Complications with surgery, such as infection, poor accessibility to the lymph node, and the possibility of missing cancerous tissue may result (Ansell, 2013). Studies have shown that this treatment initially works for approximately 67% of patients while the rest relapse after treatment. However, due to exceptionally effective salvage therapies, the overall survival rate for these patients is shown to be nearly 100% (Xing, 2013).

As far as relapsed patients are concerned, NLPHL and CHL have similar incidences of first relapses, but nearly 27% of NLPHL patients have multiple relapses.

These results have led some researchers to suggest that NLPHL is not a cancer but rather an incurable, chronic disease – though molecular biologists have proven otherwise. When an NLPHL patient relapses, he or she should immediately receive a repeat biopsy to confirm diagnosis and exclude secondary malignancies or more aggressive variants. Treatment for relapsed NLPHL patients may vary depending on age, initial treatment, response duration, staging, performance, and co-morbidities. For example, patients that were primarily treated with IFRT alone will generally be given chemotherapy or combined modality therapy as secondary treatment rather than HDCT/ASCT as in CHL. The latter is given only to select relapsed NLPHL patients because it is more toxic than other successfully proven therapies (Xing, 2013).

Emerging treatments for NLPHL include rituximab, which is an anti-CD20 monoclonal antibody. Its mechanism of action allows the drug to bind to the cells that express CD20+ in order to deliver toxic chemicals and encourage the body's own immune system to attack it. Generally, only the popcorn cells of NLPHL express CD20+, while HRS cells of CHL express the proteins CD15+ and CD30+ (Iyar, 2013). However, it has been shown that the CD20+ antigen is present in about 20-30% of CHL cases, mostly in the microenvironment of the HRS cells but also in the HRS cells themselves. Therefore, it is possible that this drug could be used to treat both major types of HL (Sweetenham, 2010). Rituximab has only proven to be effective in patients with relapsed and refractory HL, but clinical trials are currently being investigated to bring this drug to earlier stages as well as in combination with already standard therapies (Xing, 2013).

Discussion

Since the current standard primary treatments for both CHL and NLPHL are extremely effective with high overall survival rates, Hodgkin's Lymphoma is considered a potentially curable cancer. However, optimal treatment strategies depend on so much more than just the number of surviving patients. Due to the large young population at risk, treatments should also aim to reduce the risk of relapse and secondary malignancies while also reducing the risk of long-term toxicity (Xing, 2013). As a result, improved recognition of treatment-resistant HL at diagnosis as well as more powerful yet less toxic treatments are needed to improve the treatment of HL (Connors, 2012).

As seen frequently in this study, clinical trials are continuously being done to discover these optimized therapies (Xing, 2013).

Preventing Adverse Side Effects

As described earlier, a clinical prognostic factor staging system is used to determine the appropriate treatment for a patient diagnosed with HL. However, this system could be improved by further integrating biologic prognostic markers. For example, elevated levels of CD68+ macrophages and soluble forms of CD30+ antigens are both correlated to reduced progression free survival rates. Additionally, altered expression of some proteins in HRS cells may prevent apoptosis, resulting in resistance to some treatments, such as the emerging targeted therapies previously mentioned (Kadin, 2010). By analyzing biomarkers such as these, which are derived from biological fluids and tumors, the cancer's response to new drugs could be predicted, before the drugs are administered (Chabner, 2011). This could not only increase survival rates, but also reduce the risk of relapsed disease by ensuring that the patient receives the most suitable treatment plan for his or her cancer (Kadin, 2010).

Although physicians generally try to avoid giving unnecessarily toxic regimens, even the least toxic options, such as low-dose ABVD chemotherapy, may still result in severe adverse side effects. For example, neutropenia, or an abnormally low concentration of white blood cells in the blood that causes immune suppression, is a common complication of ABVD. In order to treat this side effect, therapeutic treatments such as dose modifications, the addition of colony stimulating factors, and antibiotics during treatment have been tested. However, complications may still present themselves. For example, a 15% increased incidence of bleomycin pulmonary toxicity as well as a lower 5-year survival rate has been seen among some patients taking granulocyte colony stimulating factor. Several ongoing trials are underway to confirm this data. Until then, it is important for health care providers to consistently monitor patients for acute side effects such as neutropenia (Vakkalanka, 2011).

Even if a patient successfully completes his or her primary treatment plan, the highest risks usually do not present themselves until years or even decades later. According to Thompson et al. (2011), secondary malignancies remain the leading cause of morbidity and mortality among HL survivors due to the high toxicity of many primary

treatments, primarily radiation therapy but also chemotherapy and stem cell transplants. Among these secondary cancers, those of the skin, lungs, breasts, and colon are the most frequently diagnosed. HL survivors also have increased risk of cardiovascular disease, pulmonary disease, thyroid disease, infertility, premature menopause, chronic fatigue, and psychosocial issues. However, Thompson et al. (2011) suggests that with no widely accepted guidelines available, screening and management of these health side effects is not as proficient as it could be. This in part may be due the individualized risks of each patient, which depend on the year of treatment, the type and dose of chemotherapy given, and the fields and dose of radiation given. It is therefore important that the patient and his or her future primary physicians are completely aware of the details of his or her HL treatment and the potential long-term side effects associated with it. For example, a patient treated with radiation therapy should avoid any additional unnecessary exposure, which may cause further complications (Thompson, 2011).

Additionally, by educating themselves, HL survivors could individually reduce their risk of treatment-related side effects. Survivors should continuously make healthy lifestyle choices, more frequently self-screen themselves for skin and breast cancers, start other cancer screenings earlier than the general population, and avoid live vaccines that their immune system may not be prepared for. Despite these extra precautions that HL survivors should take, most of them will only see minor, nonlethal consequences from their primary treatment (Thompson, 2011).

Controversies

After this comprehensive review of current and emerging treatments for Hodgkin Lymphoma and their associated side effects, it is important to note the numerous encountered controversial statements and viewpoints of various medical professionals. The first and most obvious is the debate regarding standard treatment types and doses for each sub-category of HL. Just as national and international organizations such as the German Hodgkin Study Group (GHSG), the European Organization for Research and Treatment of Cancer (EORTC), and the US-based National Comprehensive Cancer Network (NCCN) have varying recommendations regarding standard treatment, individual medical professionals, even within the same nation, state, or practice, may also have varying recommendations (Chustecka, 2013). For this reason, it may be

extremely valuable for patients and their caregivers to seek out second opinions from various oncologists and cancer care teams before deciding on a treatment (O'Connor, 2013)

Additionally, patients may or may not want to participate in a clinical trial for HL. Fears of uncertainty, lack of control, pain, and risk-taking could influence a patient not to take part in a clinical trial, especially if there are other already proven options available. However, among these fears, there may also be a sense of hope surrounding clinical trials, which are an attempt to find a better cure (Quinn, 2012). Dr. O'Connor stresses that clinical trials are the most important venue medical professionals have at proving the safety, efficacy, and management of diseases such as HL. He further emphasizes that every drug used to treat lymphoma, or any cancer for that matter, has undergone a clinical trial in the past (O'Connor, 2013). Dr. Ansell adds that clinical trials can significantly benefit the patient by potentially providing them with "what is considered the new and best therapy" as well as individualized scrutiny of progress in hopes of a positive outcome (Ansell, 2013). Although Dr. O'Connor and Dr. Ansell highly recommend clinical trials to their patients, other physicians may be against participation, though this depends highly on each individualized case. Nonetheless, while physician recommendations tend to be a deciding factor for patients considering clinical trials, it may be valuable for the patient to conduct his or her own research and to fully understand the benefits and risks of involvement (Quinn, 2012).

Prevailing Misunderstandings

As discussed in this paper, there are several uncertainties regarding the treatment and side effects of Hodgkin's Lymphoma that are currently being investigated. However, one of the most misunderstood aspects of this disease is what causes it. Better understanding the root causes of HL could potentially decrease the number of affected patients and as a result, the number of people experiencing complications later in life. Based on previous studies, it is known that familial factors, viral exposures, and immune deficiencies are all associated with HL, but the reason why is still misunderstood (Ansell, 2013).

It is known that siblings of HL patients, especially same-sex siblings, have a 10 times higher risk of developing HL (Ansell, 2013). Additionally, identical twins have a

higher risk than fraternal twins. These findings suggest that there could be a genetic component to the disease, but other potential factors exist as well (Ansell, 2012).

Studies have shown that the Epstein-barr virus (EBV) is present in about 40% of HRS cells in HL patients. It is believed that the clonal and malignant viral genomes that are found throughout HRS cells aid in the transformation of B-lymphocytes to cancerous cells. However, with over 90% of the world exposed to this virus and not diagnosed with HL, it is still unclear what role it plays in the disease's pathogenesis (Massini, 2009). Studies are currently investigating the histochemical nature of EBV to better understand its association with HL. Furthermore, there are several infectious illnesses such as chickenpox, measles, mumps, rubella, and pertussis that actually protect against HL, making the topic of viral exposures in regards to HL even more misunderstood (Ansell, 2013).

Finally, immuno-suppressed individuals, especially those infected with the human immune deficiency virus (HIV), have a much greater risk of developing HL as compared to the general population (Ansell 2013). HIV-positive HL patients are generally diagnosed at the advanced stage with extra-nodal involvement, poorer prognosis, and poorer outcome (Ansell, 2012). Additionally, about 90% of these patients also present positively with EBV, an association that is still unclear (Massini, 2009). Further studies should be done to better understand the root causes of HL that could potentially be used to reduce the incidence of diagnosed patients in the future (Ansell, 2013).

Conclusion

The history of the treatment of Hodgkin's Lymphoma is considered one of the greatest success stories of modern oncology (Kadin, 2010). The use of a variety of therapies including radiation therapy, chemotherapy, lymphnodelectomies, stem cell transplants, and most recently, targeted therapies, has evolved tremendously over the past several decades. Though this disease is relatively rare in the grand scheme of cancer, its advancements have proven successful and are paving the road towards a cure. According to Dr. O'Connor, this is the most exciting time in the history of treating this disease because there are now a variety of new tools and new drugs to be used (O'Connor, 2013). However, with these toxic treatments comes several severe side effects for patients that may not present themselves for years or even decades after

treatment. These side effects include secondary malignancies, heart failure, lung toxicity, chronic fatigue, infertility, impaired bone growth, osteoporosis, thyroid disorder, decreased lymphocyte count, and infection (URAC, 2008). As a result, it is vital for the emerging therapies of HL to focus not only on killing the patient's cancer, but also on reducing toxicity and the risk of secondary malignancies and complications (Xing, 2013). Clinical trials are currently the most effective way of developing these new therapies and many promising treatments are currently emerging (O'Connor, 2013).

Additionally, pre and post treatment procedures should be investigated to reduce the patient's risks. Before treatment, a better understanding of the causes of HL could reduce the number of patients requiring treatment (Ansell, 2013). Furthermore, improved histochemical diagnoses may influence alternate and more effective treatment plans (Kadin, 2010). After treatment, advanced patient and physician knowledge on the treatment given as well as consistent practice of a generally healthier and risk-conscious lifestyle, may improve the monitoring of potential side effects. Increased screenings for secondary malignancies should be practiced as well (Thompson, 2011).

Overall, more effective treatments for Hodgkin's Lymphoma, as well a variety of other cancers, are continuously being researched and developed in hopes of finding a cure (O'Connor, 2013). It is important that these treatments aim not only to kill the malignant tumors, but also to reduce long-term complications in order to provide the patient with the best outcome and overall quality of life (Xing, 2013).

Methodology Recommendations

Over 20 sources from the literature and an online conference call with medical professionals were used for the development of this paper. Many of the literature sources used were large literature reviews of the recent studies at the time. These guided me in understanding this complex topic and avoiding unnecessary information. However, a further review of each of the specific scientific studies mentioned may have been beneficial as well.

Lack of time and last minute changes to the topic of this paper made it difficult to personally interview medical oncologists and professionals. Lack of response to emails was also encountered. Nonetheless, the transcribed online conference proved to be extremely useful, especially when comparing the data to the interviewee's previous

work in the literature. The point of view of more doctors may have been more informational and less biased.

It was not until midway through the literature review that I discovered large controversies in standard treatments around the world. Reaching out to the various organizations and medical professionals within them would be an interesting comparative analysis of individual recommendations.

Problems were encountered during the initial literature review due to a misunderstanding of current and former terms used for various aspects of Hodgkin's Lymphoma. In the name itself, some articles refer to the disease as Hodgkin Lymphoma, Hodgkin disease, or Hodgkin's disease. Other examples include the names of the cancerous cells. Reed Sternberg cells are abbreviated as either HRS or RS cells and the cells of NLPHL are called lymphocyte predominant (LP) cells, popcorn cells, or lymphocytic and histiocytic (L&H) cells. These names have changed with time so older articles tend to have different names. This made finding appropriate and relevant articles difficult at times. The most up-to-date and commonly used names are used in this paper.

Though the method of data collection was successful by using NCBI's search databases and my home university's subscriptions to various journals, many relevant articles were still inaccessible without a subscription. This was a drawback to the collection of data. With more time and more resources, a more in-depth review of Hodgkin Lymphoma treatments and side effects could have been accomplished.

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Appendix I: CancerCare Conference Script

Emerging Therapies in Hodgkin's & T-cell Lymphomas

This workshop was recorded on 30 January 2013 and transcribed on 7 November 2013. The following is only a partial transcription of the data used.

Dr. Steven Ansell – Professor of Medicine at Mayo Clinic

“Thank you very much. Thanks also to everybody for being on the call. Just as I start off, I first want to say just a few words about Lymphoma in general just to paint the picture. Then as mentioned before, I’ll talk about an overview of Hodgkin Lymphoma, then emerging treatments and subsequently the role of clinical trials. So basically I think it’s important to know the Lymphoma is a cancer of lymphocytes, cells within the body that would normally fight infection have now undergone mistakes and changes and this has caused the cells to be much more aggressive in their growth pattern and much more resistant to dying off. I think it’s important also to know that there are a variety of different Lymphomas and we will be talking about some of them today, but not all of them. Broadly, these fall into two large categories, B-lymphocytes are cells that usually make antibodies and therefore, the majority of Lymphomas are B-type Lymphomas or B-cell Lymphomas. Secondly, there are other types of lymphocytes called T-lymphocytes, which very often fight infection as far as fighting viruses are concerned and as Dr. O’ Connor will later address, we will talk about T-cell Lymphomas as well. Important to know that within the B-cell Lymphoma category, there are non-Hodgkin Lymphoma and Hodgkin Lymphomas and we are going to be talking in a minute about Hodgkin Lymphoma. This is a disease characterized by what is called the Reed-Sternberg cell, which is a cancer cell that recruits a lot of other cells around it to help with its growth pattern.

So with that, I’d like to talk a little bit about Hodgkin Lymphoma specifically and as I mentioned earlier then take it into emerging treatments and the role of clinical trials. So firstly, I think as far as Hodgkin Lymphoma is concerned, it’s important to know that this is a relatively uncommon disease. It affects about 9,000 new patients in the United States every year and it’s a disease that is often found in young adults, often in patients in their 20s, but there’s also a further group of patients, the 55 years and older, who can also get the disease. The risk factors for this disease include familial factors, viral exposures, and immune suppression. To talk about that a little bit further, when studies have been done on family members of patients who have had Hodgkin Lymphoma, same-sex siblings of patients with Hodgkin Lymphoma have a 10-fold increased risk of developing Hodgkin Lymphoma and the cause for that is really not well understood. Equally poorly understood is the role of viruses in this disease and the reason that may be important is that often Epstein-Bar virus is found to be associated with patients that have Hodgkin Lymphoma and often the virus is actually incorporated into the genetic material. But many people in the world are exposed to this virus and don’t get Hodgkin Lymphoma and therefore it’s not entirely clear as to what this virus may be doing. Other viruses, more common

viruses, actually can be protective against Hodgkin Lymphomas, so the whole role of viral exposures is still unclear. What is much more clear though, is that people who develop immune suppression are at significant risk, so those that have infections with the human immune deficiency virus, HIV virus, have a significant increased risk of developing Hodgkin Lymphoma.

Important to know that typical symptoms of this disease are patients present with larger lymph nodes often above the diaphragm so often in the neck, sometimes in the chest, often above the clavicle, or in the auxiliary armpits. Less commonly but also seen are groin lymph nodes and intra-abdominal lymph nodes. About a third of patients when diagnosed present with systemic symptoms, meaning they get high fevers, they get drenching sweats, they lose a lot of weight unintentionally, and although not really a constitutional symptom, a lot of patients present with significant itching that isn't well explained by other reasons. To make the diagnosis of Hodgkin Lymphoma, you have to get a biopsy and it's important that an excisional biopsy be done, in other words a whole lymph node be taken out because as I mentioned earlier, the Reed-Sternberg cell is a cell that we want to identify under the microscope and there can be a lot of inflammatory cells and so if one only takes a very small sample, this can be a difficult diagnosis to make. This is an interesting disease because the tumor cells are actually in the minority and much of what is seen in the biopsy are inflammatory reactive cells.

There are two large categories within Hodgkin Lymphoma, most people get what is called Classical Hodgkin Lymphoma, but there is a less common, in fact quite rare variant, called Nodular Lymphocyte Predominant Hodgkin Lymphoma. Once a diagnosis has been made when one is seen by your physician, the first order of business and very important for your future management is staging of the disease. This is critical because it is used in the decision-making for treatment and a PET scan is also often done along with a bone marrow in some patients to determine where in the body the disease currently is active. That will help to define, as I'll mention in a minute, exactly what therapy needs to be given. Something that will tell your doctor as to whether your disease is going to cause more trouble or less trouble down the line has to do with the amount of disease, or what we call disease bulk, so people that have very large mediastinal masses, or masses in their chest or multiple different sites of disease or a lot of abnormal blood tests. These can be predictive of a disease that will be more likely to be aggressive.

Switching gears then to talking a little bit more about standard therapy, the initial therapy as I mentioned before is driven in large part by where in your body the disease is present. Patients are categorized into early stage, in other words just one side of the diaphragm, or more advanced stage, meaning more diffuse throughout the body. Early stage patients, based on those prognostic factors or factors that tell one about how the disease is likely to behave, are further categorized into what we call favorable disease or unfavorable disease. So for

patients that have early stage disease, have the most common approaches to do what is called a combined modality therapy, in other words patients receive a short course of chemotherapy and then receive what involves field radiation therapy just at the sites of enlarges lymph nodes. Patients that have more advanced disease will commonly receive only chemotherapy and no radiation treatment. The favorable or unfavorable categorization of limited stage disease allows us to limit how much chemotherapy one needs and how much radiation one needs. So, those that are in a very favorable category may only receive 2 or 3 cycles of chemotherapy followed by radiation vs. those in unfavorable categories who will receive more cycles, typically 4 cycles of treatment. Patients, who have advanced disease, typically receive ABBD chemotherapy for at least 6 cycles of treatment. But for those that have a number of pore prognostic features, they may require more aggressive treatment and other therapies such as AB/COP combination is considered.

Lastly is the disease actually recurs after initial treatment, a common approach thereafter is the treat people with high doses of chemotherapy and autologous in-cell transplant. Autologous in-cell transplant means using your own stem cells to rescue after the high dose of chemotherapy. So that in just a few sentences is an overview of Hodgkin Lymphoma. I wanted to mention as a second point then emerging treatment in Hodgkin Lymphoma. I think it's important to know that a number of new drugs are being tested in Hodgkin Lymphoma and are shown to have significant activity. Hodgkin Lymphoma is commonly positive for a protein on the cell surface called CD-30 and a new antibody drug conjugate called Brentuximab vedotin binds to CD-30 and delivers chemotherapy into the cell. That has resulted in a very high response rate in patients that have had the disease come back even after undergoing an autologous stem cell transplant. Other treatments include therapies such as Panobinostat or Lenalidomide or Everolimus. These therapies target or interfere with messaging pathways or with the support structure around the cancer cell and again the patients that have had autologous transplants have shown significant benefit. So these are therapies that are now being moved earlier in the disease course and being added to some of the standard treatments I mentioned just a little bit ago.

Finally, I just wanted to talk about the role of clinical trials. So, I think what is very important, as we understand the disease is to then understand what is the best therapy and the standard treatments that are currently used are standard in that they have been tested in clinical trials. As we move forward, have patients and physicians participating in clinical trials, allow us to really confirm that these drugs can be safely administered on their own or can be safely combined with other therapies and then can be compared to the standard therapies to hopefully show superiority as far as the number of patients that benefit and the durability of that benefit. My recommendation always to patients is to consider participating in a clinical trial because not only would you potentially receive what is considered the newest and best therapy, you will also receive very close scrutiny of your

progress in the hopes of providing you with the very best outcome. So with that I will stop and pass in back to the chairperson.”

Dr. Owen O'Connor – Professor of Medicine and Experimental Therapeutics; Director for the Center of Lymphoid Malignancies; Co-director for the Program of Lymphoid Development and Malignancies at Herbert Irving Comprehensive Cancer Center at Columbia University Medical Center – The New York Presbyterian Hospital

“Clinical trials, I can’t stress enough, are the most important venue we have at the moment in terms of trying to prove our management of these diseases. Every drug that we use to treat Lymphoma, is a drug that at some point in its history was studied in a clinical trial. And because many of the standards of care for these diseases leave us wanting to do a little bit better, the need to put patients on clinical trials is incredibly important for the physicians as well as the patients...”

...While these are complex diseases that are relatively rare, I actually think this is probably the most exciting time in the history of these diseases to be involved in treating them because we at long last have a variety of new tools and a variety of new drugs and the challenge now on both the patient part and the professional treating physician part will be to try to get as many patients as we can in these clinical trials so we can more rapidly make progress towards improving the outcome of the management of these diseases...”

...So the lymphatic system is a network of small vessels that connects various lymph nodes throughout the body. It often runs in parallel with the veins of the body. The lymphatic system plays a critical role in your immune system and it is also the site where many of the lymphocytes that are born in your bone marrow, that exit the bone marrow, circulate in your blood and they actually land in various lymph nodes around that body and these lymph nodes are major centers of higher education if you are a lymphocyte. It’s where lymphocytes learn how to be hard caring members of your immune system and they learn how to recognize discrete kinds of antigen towards infections so the if you get exposed, your body’s immune system is allowed to mount a response. So the lymphatic system is just this broader network of interactions between your lymph nodes, your spleen, and other lymph node tissues throughout the body that all play a central role in educating and trafficking lymphocytes so they can be a functional part of your immune system.”

Dr. Steven Ansell – Professor of Medicine at Mayo Clinic

“As I mentioned in my presentation, knowing exactly the extent of the disease in one’s body is critical to really being able to define a good treatment plan. So common tests that are done for what appear to be clinical stage IIA Hodgkin Lymphoma include a staging evaluation using CAT scans and PET scans, sometimes they are combined CT scans that does it all at once is a very common and important test. Additionally, in some patients, if more extensive, a bone marrow test will also be done to exclude the possibility of cells present in the bone

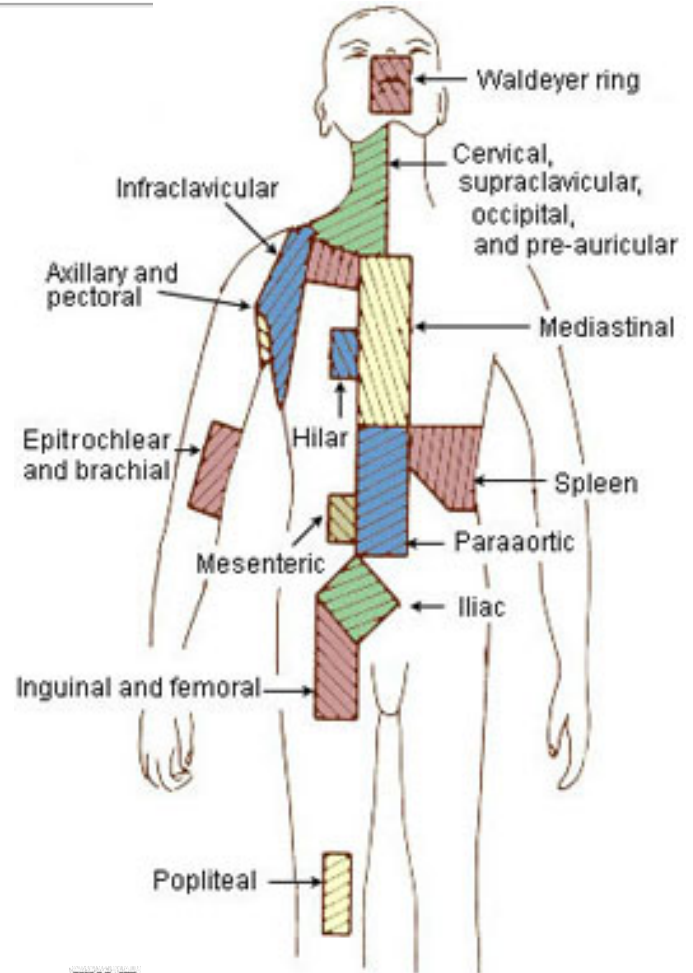
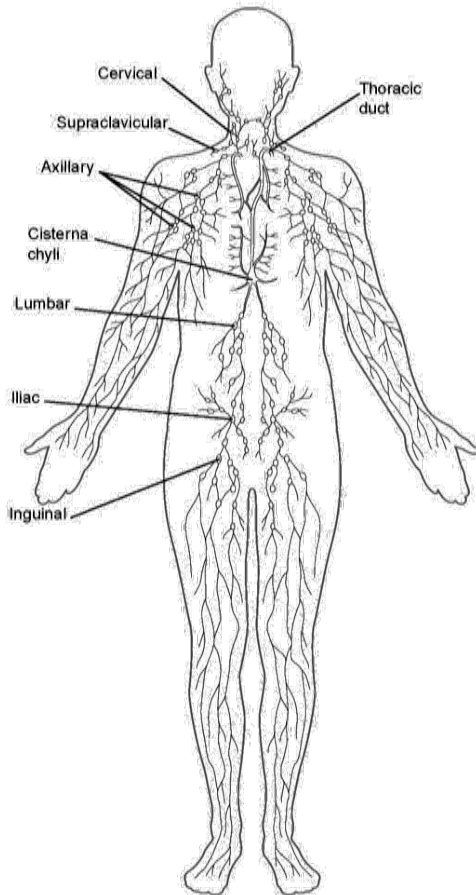
marrow. Additionally, blood work is done to really understand if there are any features to suggest that the disease is going to be more badly behaved or well behaved and those can include the number of lymphocytes, the hemoglobin, and other tests in the blood. And additional tests that are often are just to make sure that the heart function and lung function of the patient are adequate as one considers giving treatment can affect that, and that can include heart test for the injection fraction or the strength of the heart with the pumping action via way of a MUGA scan or an echocardiogram and sometimes pulmonary function testing to see how well your lung function is, is also done. So those are the common standard therapies, and I guess I would add one other thing, and that is in young patients, before getting chemotherapy, consideration for preservation of fertility is also important and so often that is addressed as well.”

Appendix II: Lymphatic System Diagrams

Images used to create Figure 2 in the text

 **Full Body**
Lymphatic System - Anterior View

Anatomical Line Drawings



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