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Advancements in the Treatment for classic Hodgkin Lymphoma

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INTRODUCTION:

In the United States, between the years 2011 and 2015, 42,490 cases of classical Hodgkin Lymphoma (cHL) were reported, and 5,585 people died.[1] While the response rate to initial treatment leading to remission for those diagnosed with cHL has increased, a portion of patients with remitting or refractory Hodgkin Lymphoma (RRHL) continue to require attention. Currently, the Centers for Disease Control and Prevention estimates a 5-year survival rate for those with Hodgkin lymphoma of 83.5%, leaving 16.5% either in relapse or remitting disease.[1] As research surrounding the treatment of cHL increases, there has been an emergence of utilizing novel treatments to help expand and improve clinical outcomes. These novel treatments not only include improvements in efficacy, but also in the reduction of adverse events leading to further morbidity. Long term side effects from primary treatment include heart disease, lung disease, other forms of cancer, and infertility.[2] Several advances in the understanding of Hodgkin Lymphoma have opened doors to new therapies designed to improve those with RRHL, as well as to reduce short-term and long-term side effects. Novel treatments offer options that improve efficacy while limiting adverse events when compared to standard treatments.

BACKGROUND:

Current treatment for cHL is determined by several factors, primarily the stage of disease, associated bulky disease or b-symptoms (weight loss, fever, etc.), the patient's age and other biometrics. Treatment for stage I/II usually begins with chemotherapy and sometimes also includes radiation therapy. For stage III/IV or more advanced disease, a more aggressive

chemotherapy approach is indicated. The most common chemotherapy regimen for stage III/IV disease in the United States is Adriamycin (doxorubicin), Bleomycin, Vinblastine, Dacarbazine (DTIC), also known as ABVD. Other therapies include BEACOPP or Stanford V, which are predominantly used in Europe.

Current staging involves utilizing positron emission tomography (PET) scans to identify the spread of the disease at time of diagnosis and throughout treatment. This helps to establish the severity of the disease as well as determine the strategy for treatment. Depending on the stage, physicians may use chemotherapy, radiation therapy, or other combination therapies may be utilized to combat the disease. Currently, the algorithm to determine treatment strategies based on PET scans is rigid, and they have limited response rates and efficacy. Yet, patients continue to respond to initial treatments, as well as go into remission. Novel therapies may help to broaden the strategies to better target the disease specific cells as well as reduce secondary disease burden.

So, what are novel therapies, and how do they work? Novel treatments include targeted therapies that utilize the genetic and cellular makeup of cHL. Using cellular morphology and genetic markers to target the microenvironment or the replication of the diseased cells themselves are some of the ways these novel therapies work. Examples include immune checkpoint inhibitors, chimeric antigen receptor T-cell therapy, and monoclonal antibodies, which may someday take the place or be used as adjunctive therapy.[3]

DISCUSSION:

Current standard treatments are associated with several adverse effects

Current standard treatments carry several long-term complications and increase the risk of disease burden and are therefore suboptimal strategies. One group of researchers examined disease burden in a 40 year follow up and compared it to the general population not treated for cHL.[4] This retrospective study examined over 2,000 individuals who had been diagnosed with cHL before the age of 51 and who also had a 5-year survivorship after initial diagnosis. Patients were selected from the 1960s to the 1990s, and several treatment strategies were included as comparison, ranging from primarily radiation therapies in the '60s and '70's to more advanced chemotherapy treatments in the '80's and '90's, including ABVD.

Measuring data from medical records and general practitioners from several Dutch university hospitals, researchers found that there was a 4-to-6-fold increase in cardiac events compared to patients in the general population. Those treated earliest (before age 25) showed the greatest increase in cardiac events. At 40 years after diagnosis, the overall incidence of cardiovascular disease (including coronary artery disease (CAD), valvular heart disease (VHD) or heart failure (HF)) was 49.5% compared with 24.7% in patients not receiving any form of treatment. This clearly shows an increased risk of cardiac risk associated with treatment, which investigators further equated to 70 and 58 excess cases of CAD and HF, per 10,000 person years, respectively.[4] This research shows that over a long period of time, and through various changes in the treatment strategies, there still are some very serious risks associated with even the most up to date treatments.

Not only do standard treatments for cHL include increased risk for heart related issues, but more specifically ABVD carries significant pulmonary complications associated with its use as standardized treatment, most specifically bleomycin. In a phase 1 open label trial comparing a newly developed novel treatment, brentuximab vedotin (BV), combined with the standard treatment ABVD and showed a 44% rate of pulmonary complications compared to 0% in patients receiving BV +AVD (BV in lieu of bleomycin).[5] BV (a CD30 monoclonal antibody), has shown promising results in RRHL and this study began investigating the safety profile of BV as first-line treatment. The researchers enrolled 51 patients all treatment naïve and newly diagnosed with either stage II bulky disease or stages IIB-IV. Each patient was enrolled sequentially into either the standard ABVD treatment or the modified standard treatment (AVD). Both groups were then dose escalated with BV to determine the safety profiles for each group. Adverse reactions were then recorded in each group, which consisted of neutropenia, anemia, fatigue, pulmonary toxic effects, among others. One major finding was that the group with ABVD and BV recorded pulmonary toxic effects (11 of 25 participants, or 44%) compared to no participants in the AVD and BV group (0 of 26 participants). Researchers pointed out that the addition of BV to standard treatment increased the historical rate of pulmonary toxic events, and concluded that BV should not be given in combination with bleomycin.

These findings highly suggest that BV is a very safe medication that may be used in place of bleomycin, to help reduce pulmonary toxic events. What is also of importance, is that in both groups of the study, nearly all participants achieved remission, showing that BV is just as effective in the treatment of cHL as initial therapy. As of March 2018, the FDA approved brentuximab vedotin (Adcetris®) as a first line agent in combination with chemotherapy for

stage III-IV cHL.[6] With this approval, patients are now able to choose a treatment plan that may reduce their risks of suffering a serious adverse event.

It is certainly clear that chemotherapy carries risks, and that more advances are being made with novel treatments to help mitigate and minimize the risk profile of such treatments. It is important to then focus on the effectiveness of these new medications. How likely are they to improve efficacy and allow patients to achieve full 5-year remission?

Novel therapies are effective

Researchers have sought to answer those questions, and several have found that novel treatments have similar or higher efficacy in both RRHL and may be useful as first-line agents in combination or in lieu of chemotherapy. A phase II study of BV evaluated the safety profile as well as it's efficacy in patients with RRHL.[7] This study investigated participants in RRHL who failed prior intense chemotherapies as well as stem cell transplantation. In this group of 102 participants, 33% achieved complete remission, and they had a low adverse effects profile that was manageable. These results allow for providers to offer further treatment plans in the face of remission or failed initial response and gives hope to those who carry the disease. However, due to the favorable side effect profile and similar, if not better, response rates, it also led researchers to further extend investigations earlier in the treatment plan.

This study, along with the previously discussed phase I open label study combining BV with AVD as well as ABVD, prompted researchers to investigate a randomized open label phase III trial comparing BV and AVD vs ABVD alone as a first line treatment for stage III/IV cHL[8], known as the ECHELON-1 international trial. This specifically examined the novel treatment as

first-line for advanced stage disease. Participants were selected as advanced stage with treatment naïve profiles and enrolled randomly to receive the standard ABVD treatment or the AVD + BV treatment protocols. Overall, the study showed that BV and AVD had a 4.9% lower risk of disease progression, death or non-response and had better efficacy. This measured progression-free survival at 2 years and clearly showed that not only did the AVD+ BV group have a lower risk of side effects, but fewer patients died from any cause (9 vs 22 deaths, respectively). This large-scale study across multiple nations clearly established that there are more effective treatments available, and that they carry a lower risk of adverse events. With this addition, BV has opened doors to other possible treatment avenues, based on the biomarkers present in each individual.

Other novel therapies are under investigation

There are several novel therapies that may be utilized and are under further investigation in their role in cHL treatment algorithms. As discussed previously, targeting Hodgkin lymphoma cell lines, particularly those that express the CD30 cell line, as with BV, is very promising. cHL has the classic cell identifier as the Reed Steinberg cells (H-RS), which, although the overall production of these cell types are small, are nonetheless critical in managing and treating individuals with cHL. These cells also express other receptors including CD15 and CD20, which have undergone much investigation as to their usage, offering much promise.

One such research study examines the programmed death (PD-1) blockade as a potential avenue to help patients with RRHL.[9] The overexpression of the PD-1 ligand on the

malignant Reed-Steinberg cells in Hodgkin's lymphoma allows for these cells to evade the normal immune response, making this pathway a potential target to expose and blockade. This phase 1 study investigated the PD-1 blockade using the drug nivolumab after patients had received and failed (relapsed or remitted) first line treatments (including standard chemotherapy, stem cell transplantation, and BV). Though the number of participants were small, results were promising and showed very low adverse events. Responses were included as complete response, tumor progression or excessive toxic effects. Of the 23 participants in the study, 20 achieved a complete or partial response, with the remaining 3 acquiring stable disease. The rate of progression free survival at 24 weeks was 86%. With these figures, the researchers concluded that the PD-1 blockade may help provide another avenue to treat Hodgkin's lymphoma.

Another potential avenue, not too dissimilar from the BV $CD30^+$ pathway, is the $CD20^+$ pathway, as targeted by the drug rituximab. One study examined the biological effects of this drug in combination with the standard treatment ABVD in patients newly diagnosed with cHL and treatment naïve.[10] The researchers noted that previous information about the Hodgkin's Reed-Steinberg line had a small population with a memory B-cell phenotype that would generate and sustain the growth of the H-RS cells. Though a small population, and not always expressed, presence of these B-cells often indicated a higher rate of remittance to standard treatments. With this in mind, researchers conducted a phase II study with newly diagnosed patients with cHL of stage IIB-IV. By adding the drug rituximab to the standard ABVD treatment, researchers were able to evaluate whether the B-cell phenotype was still present after treatment to better determine prognostic factors. Results of this single arm study were

promising. Analysis of the blood samples taken prior to treatment initiation showed that 21 of the participants exhibited the B-cell phenotype prior to treatment, and after the rituximab treatment, 19 had no detectable signs of the B-cells. Further, the safety profile was favorable, with an estimated event-free survival (EFS) at 3 years of 83%, and overall survival of 98%. This shows great promise in possibly managing patients with cHL using other chemotherapy drug combinations.

Another potential pathway to target involves utilizing oncolytic viruses to kill the growth of H-RS cells. One study examined the role of the measles virus (MV) as well as vesicular stomatitis viruses (VSV) to target the $CD30^{+}$ cell line[11]. These two viral strains were utilized in vitro and en vivo to demonstrate their potential effects. The results showed promise in killing and preventing the growth of cHL cell lines, particularly for the VSV. While this is a drastically new approach, it too has created other potential methods in targeting cHL cells, and thereby may overhaul the way treatment algorithms are determined.

CONCLUSION:

It is clear that current standard treatment for cHL has its disadvantages, and novel treatments are showing promising signs of similar efficacy with lower adverse effects risk profiles. Chemotherapy and radiation therapy have a long history of serious complications, and while treatment success rates remain high for cHL patients, there are still those who require further avenues to achieve remission and improve quality of life. Most research is focused on initiating these treatments as second or third line, after standard therapies (ABVD, autologous stem cell transplantation, etc.) either don't respond or patients relapse. Further analysis of

individual patient biological markers needs to be investigated in order to develop better treatment algorithms. As these developments come to light they may very well help to increase the clinical response and reduce rates of relapse/remittance while also minimizing further disease burden, having profound implications clinically.

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