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Review Article

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STANFORD V REGIMEN OVER ABVD REGIMEN IN HODGKIN'S LYMPHOMA

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ABSTRACT

Hodgkin lymphoma (HL) is a rare malignancy of the lymphatic system, particularly prevalent among young adults. In Hodgkin's lymphoma, treatment approaches have advanced, with both the ABVD regimen and the more intensive Standard V regimen serving as primary options. The Standard V regimen, noted for its dose-dense strategy, shows promise particularly for patients with advanced or high-risk disease, potentially achieving higher remission rates and extended progression-free survival. While ABVD remains favored for its proven effectiveness and manageable side effects, Standard V's intensified approach increases hematologic toxicity, impacting patient quality of life. Deciding between these regimens often involves weighing efficacy against toxicity, tailored to each patient's condition.

INTRODUCTION

Hodgkin lymphoma (HL) is a rare malignancy of the lymphatic system, particularly prevalent among young adults. Characterized by a few malignant B-lymphocyte-derived cells within a robust inflammatory environment, the exact mechanisms behind HL remain only partially understood despite extensive research.[1] Epstein–Barr virus (EBV) infection is associated with some cases, and both genetic factors and HIV infection serve as independent risk factors. Histologically, HL is divided into two main categories: about 95% of cases are classified as classic Hodgkin lymphoma (cHL), encompassing nodular sclerosis, mixed cellularity, lymphocyte-rich, and lymphocyte-depleted subtypes. The remaining 5% represent nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL).[2] Classic HL is defined by the presence of Hodgkin and Reed-Sternberg (HRS) cells, which are CD30-positive and typically surrounded by a mix of inflammatory cells.[3-4] Conversely, NLPHL is marked by lymphocyte-predominant (LP) cells, expressing CD20 but lacking CD30, within an environment largely made up of mature lymphocytes. Clinically, HL often presents with painless lymph node enlargement, especially in areas like the neck, armpits, or groin, and may also involve systemic symptoms, including fever, night sweats, weight loss, itching, and fatigue. Diagnosis is established through physical examination, imaging (such as CT or PET scans), and lymph node biopsy to identify characteristic cells.[5-6] Treatment strategies for HL depend on disease stage and patient-specific factors, typically involving chemotherapy, with the ABVD regimen (doxorubicin, bleomycin, vinblastine, and dacarbazine) as a standard option. Radiation therapy and, in certain cases, stem cell transplantation are also employed, especially for relapsed cases. The prognosis for HL is generally favorable, with a five-year survival rate near 85%, though individual health factors and disease specifics influence outcomes.[7] Long-term monitoring is critical due to the potential for late effects from treatment, such as secondary cancers and cardiovascular issues. Among the primary treatment regimens, ABVD and Stanford V are well established, though they differ in dosing, intensity, and side effects. ABVD has long been considered the standard care in Hodgkin lymphoma, valued for its efficacy and manageable side-effect profile, making it widely accepted in clinical practice.[8] The Stanford V regimen, developed as a more intensive treatment, offers potential benefits for advanced cases through its shorter duration and higher dosing intensity.[9] This review explores the clinical outcomes associated with both regimens, evaluating their comparative effectiveness, safety, and impact on patients' quality of life. By examining the advantages and limitations of each, the goal is to provide insights that support personalized treatment choices in Hodgkin lymphoma and contribute to ongoing research aimed at refining therapeutic options.

Stanford v regimen[10-12]

The Stanford V regimen is a chemotherapy protocol used in the treatment of Hodgkin lymphoma, particularly in patients with bulky or advanced-stage disease. Developed at Stanford University, it aims to provide effective treatment with a relatively short course of therapy, often followed by radiotherapy to sites of bulky disease. This regimen is distinct for its multi-agent

approach and shorter treatment duration compared to other regimens like ABVD or BEACOPP.

Standford regimen includes Mechlorethamine Hydrochloride, Doxorubicin Hydrochloride, Vinblastine Sulfate, Vincristine Sulfate, Bleomycin, Etoposide Phosphate and Prednisone.

Treatment duration - The Stanford V regimen for treating Hodgkin lymphoma typically involves a treatment duration of approximately 12 weeks, administered in cycles. The regimen consists of six cycles of chemotherapy, with each cycle lasting two weeks. The drugs used in the Stanford V regimen include doxorubicin, bleomycin, vinblastine, and dacarbazine, often accompanied by prednisone. Treatment response is closely monitored, and adjustments may be made based on individual patient needs and response to therapy. Following the completion of the chemotherapy cycles, patients may undergo additional therapy such as radiation depending on their response and specific clinical circumstances.

Mechanism of action - The mechanism of action involves the synergistic effects of these drugs to target and kill rapidly dividing cancer cells. Doxorubicin intercalates DNA and inhibits topoisomerase II, leading to DNA damage; bleomycin generates free radicals that cause oxidative damage to DNA; vinblastine disrupts microtubule formation, preventing mitosis; Etoposide also inhibits topoisomerase II, further impeding DNA replication. Mechlorethamine is an alkylating agent that cross-links DNA, disrupting replication and transcription. Bleomycin can cause DNA strand breaks via oxidative damage. This multi-drug approach maximizes tumor cell kill while attempting to minimize resistance and side effects associated with monotherapy.

Side effects - The Stanford V regimen, a chemotherapy treatment for Hodgkin lymphoma, is associated with several potential side effects due to its combination of drugs. Common side effects encompass myelosuppression, leading to decreased blood cell counts, which can result in anemia, increased risk of infection, and bleeding issues. Patients may also experience nausea, vomiting, fatigue, hair loss, and peripheral neuropathy. Additionally, bleomycin can cause pulmonary toxicity, leading to cough and shortness of breath, while doxorubicin is associated with cardiotoxicity, particularly at higher cumulative doses.

Advantage and disadvantages - The Stanford V regimen, a chemotherapy protocol for treating Hodgkin lymphoma, offers several advantages and disadvantages. One of the main advantages is its ability to provide effective treatment with a relatively short duration, typically around 12 weeks, which is beneficial for patient compliance and reduces treatment-related fatigue. It combines multiple agents, including doxorubicin, bleomycin, vinblastine, and dacarbazine, which enhances its efficacy against the disease. However, its disadvantages include potential side effects such as myelosuppression, pulmonary toxicity from bleomycin, and increased risk of secondary malignancies.

Literature review - The Stanford V program is a brief (12 weeks) weekly chemotherapy program, supplemented in most patients with involved-field radiotherapy (IFRT) given to sites originally ≥5 cm and/or to macroscopic splenic disease. The objective is to maintain or improve the outcome of patients with locally extensive/or advanced HL while minimizing both short- and long-term toxicity. At Stanford, the 5-year FFP was 89% and OS was 96%. The program was well tolerated, with no pulmonary toxicity.[13-14]

Edwards-Bennett SM et al. 2010 conducted a study in Stanford V program for locally extensive and advanced Hodgkin lymphoma and results shows that 97% of patients completed the 12-week Stanford V chemotherapy course. Stanford V with appropriate radiotherapy is a highly effective regimen for locally extensive and advanced HL.[15] Abuzetun JY et al. 2007 conducted a study concluded that Stanford V Regimen Is an Effective Treatment for Good Prognosis Patients with Hodgkin's Disease.[16-17] Advani R et al. 2012 conducted a study and concluded that excellent efficacy of an abbreviated Stanford V regimen in patients with early-stage Hodgkin lymphoma.[18]

Abvd chemotherapy[19-22]

The ABVD regimen is a common chemotherapy protocol used to treat Hodgkin lymphoma, particularly in early-stage and advanced-stage cases. ABVD abbreviated as Adriamycin (doxorubicin), Bleomycin, Vinblastine and Dacarbazine.

Drugs and dose with treatment duration - A typical cycle of ABVD chemotherapy is administered over a four-week period, consisting of two doses: the first dose is given on day 1 and the second on day 15. All four chemotherapy agents are delivered via intravenous infusion. Generally, ABVD chemotherapy is provided in an outpatient setting, meaning that hospitalization is not necessary.

- Doxorubicin: 25 mg/m² IV
- Bleomycin: 10 units/m² IV
- Vinblastine: 6 mg/m² IV
- Dacarbazine: 375 mg/m² IV

Mechanism of action - The ABVD regimen employs a combination of agents that utilize diverse mechanisms to effectively target and eliminate malignant cells. Doxorubicin intercalates into DNA, disrupting the function of topoisomerase II and leading to DNA strand breaks; Bleomycin causes oxidative damage to DNA through the generation of free radicals, resulting in cell death; Vinblastine inhibits microtubule formation, thus preventing mitosis; and Dacarbazine, an alkylating agent, forms covalent bonds with DNA, leading to cross-linking

and further hindering DNA replication. By incorporating multiple drugs with unique actions, ABVD enhances its therapeutic efficacy while reducing the likelihood of resistance. This multi-agent strategy enables the targeting of cancer cells at different stages of the cell cycle, positioning it as a highly effective treatment option for Hodgkin lymphoma.

Side effects - Hair loss, myelosuppression, Nausea and vomiting, Neuropathy, Infertility, Pulmonary toxicity, Cardiac toxicity.

Advantages and disadvantages - Advantages of ABVD include its effectiveness in achieving high response rates, especially in early-stage disease, and its relatively favorable side effect profile compared to older regimens, which allows for better tolerability in patients. Furthermore, it is administered on an outpatient basis, providing convenience for patients. However, disadvantages include the potential for significant side effects such as pulmonary toxicity (particularly from bleomycin), myelosuppression leading to increased infection risk, and the risk of secondary malignancies due to the alkylating agents involved.

Literature review - Current international guidelines recommend ABVD alone or in combination with radiotherapy for early-stage disease and ABVD alone for advanced-stage disease.[23] In limited-stage non-bulky HL, ABVD alone confers an 87% 12-year freedom from progression in high-income countries (HICs).[23] In advanced disease, ABVD is associated with 5-year failure-free survival rates of 61%-63%.[24] Deboer JR et al. 2020 concluded that seventy-three patients initiated ABVD, and 54 (74%) of these completed all 6 cycles.[25] A study conducted by Makiyama J et al. 2020 concluded that ABVD with dose attenuation may represent a feasible and effective strategy for the treatment of older patients with CHL in clinical practice, particularly in those with early-stage disease.[26] A study conducted by Mponda et al. concluded that treatment with ABVD is safe, efficacious, and affordable for HL in Malawi. Outcomes are worse than in high-income countries due to HL progression.[27] Boleti E et al. 2007 concluded that ABVD administration irrespective of granulocyte counts allowed the treatment to be given at full dose without delays or significant number of infective episodes.[28] Rueda Domínguez A et al. 2004 concluded that administration of six ABVD cycles is an effective and safe treatment in patients with stage I and II Hodgkin's lymphoma.[29]

Standford v regimen vs abvd therapy in hodgkin lymphoma

In Hodgkin lymphoma, both the Stanford V regimen and ABVD therapy are standard chemotherapy approaches, each with distinct protocols and implications. The Stanford V regimen is an intensive, shorter-duration protocol consisting of doxorubicin, vinblastine, mechlorethamine, vincristine, bleomycin, etoposide, and prednisone, typically administered over 12 weeks. It often incorporates radiation therapy for bulky disease, aiming for rapid response and shorter treatment time.[17] ABVD, on the other hand, is a less-intensive, longer-duration regimen, consisting of doxorubicin, bleomycin, vinblastine, and dacarbazine administered over 6-8 months. ABVD is widely used due to its efficacy and manageable toxicity profile, making it a favored choice for many patients. Studies show similar efficacy in terms of survival, but differences in toxicity and treatment duration may influence the choice of regimen. Stanford V may result in increased peripheral neuropathy, while ABVD is associated with pulmonary toxicity due to bleomycin.[21] Gordon L et al. 2012 concluded that no significant difference in the overall response rate between the two arms, with complete remission and clinical complete remission rates of 73% for ABVD and 69% for Stanford V. At a median follow-up of 6.4 years, there was no difference in FFS: 74% for ABVD and 71% for Stanford V at 5 years.[30] In the British randomized study comparing ABVD and Stanford V treatments in 520 patients, Hoskin et al. found no significant difference in failure-free survival (FFS) or overall survival (OS) between the two groups. Initially, both treatment groups included radiation as per the Stanford V protocol, but later in the ABVD group, radiation was limited to patients with bulky mediastinal disease. In the Stanford V group, 73% received radiation, while only 53% did so in the ABVD group. Response rates were 91% for Stanford V and 92% for ABVD. After a median follow-up of 4.3 years, the estimated 5-year FFS and OS were 76% and 90% for ABVD, and 74% and 92% for Stanford V, respectively.[31] Chisesi T et al. 2002 concluded that ABVD gave superior results to Stanford V in terms of response, low relapse rate and failure free survival. Patients treated with Stanford V did the worst compared with those treated with ABVD.[32] Gobbi PG et al. 2005 concluded that ABVD were superior to Stanford V chemotherapy in terms of response rate and FFS and progression-free survival. Stanford V was more myelotoxic than ABVD. ABVD is still the best choice when it is combined with optional, limited irradiation.[33]

CONCLUSION

In conclusion, the efficacy of the Standard V regimen with the ABVD (Adriamycin, Bleomycin, Vinblastine, Dacarbazine) regimen for Hodgkin's lymphoma, the evidence ultimately favors the ABVD regimen. Despite the more aggressive approach of the Standard V regimen, which includes additional chemotherapeutic agents, ABVD demonstrates a balance of high efficacy with a more favorable toxicity profile, making it more tolerable for patients over extended treatment cycles. Furthermore, ABVD has shown consistent, competitive outcomes in terms of remission rates and long-term survival across various clinical trials, solidifying its status as a first-line therapy for Hodgkin's lymphoma. This regimen's win over Standard V in terms of overall patient outcomes and quality of life has contributed to its widespread acceptance as the preferred treatment standard.

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