MODULE 3

LEARNING OBJECTIVES

This module is a part of an e-learning program which focuses on the different aspects of brentuximab vedotin, pivotal clinical trials with brentuximab vedotin, role and approval for use in certain patient populations which include patients with relapsed or refractory Hodgkin's lymphoma and patients with relapsed or refractory systemic anaplastic large-cell lymphoma. The material presented as part of this e-learning program is strictly for internal training purposes only.

This presentation will help you understand the mechanism of action of brentuximab vedotin and its role in management of relapsed or refractory Hodgkin lymphoma.

At the end of this module you should be acclimatized with the pivotal phase II trial of brentuximab vedotin in individuals with relapsed or refractory Hodgkin lymphoma.

You should be aware of the key components of the trial including the materials and methods, results and conclusions.

INTRODUCTION

The standard of care for patients with relapsed or refractory Hodgkin's lymphoma (HL) is salvage chemotherapy followed by autologous stem-cell transplantation (ASCT) which can induce long term remissions in approximately 50% of patients.[1]

For patients who experience relapse or progressive HL within 1 year after ASCT, the prognosis is exceedingly poor, with a median post-progression survival of 0.98 years.[2]

The population of patients who relapse after ASCT or chemotherapy and are ineligible for ASCT has no currently available standard of care and represents an urgent unmet medical need.[1]

Brentuximab vedotin is a novel CD-30 targeted antibody drug conjugate which is indicated in such patients.[3]

PIVOTAL PHASE II TRIAL IN RELAPSED OR REFRACTORY HODGKIN LYMPHOMA POST ASCT

A phase II trial with brentuximab vedotin was conducted with patients who had relapsed or refractory HL and had undergone prior autologous stem cell transplantation (ASCT).[1]

102 individuals who were 12 years or older were included in the study and brentuximab vedotin was administered at 1.8 mg/kg intravenously over 30 minutes every 21 days for up to 16 cycles.[1]

The patients Hodgkin's lymphoma was reassessed at 2, 4, 7, 10, 13, and 16 cycles by an independent reviewer facility (IRF).[1] The patients were then followed-up every 12 weeks.[1]

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BRENTUXIMAB VEDOTIN STUDIED IN A HEAVILY PRE-TREATED POPULATION

The median age of the patients with HL who entered this Phase II trial was 31 years.[1]

Brentuximab vedotin was studied in a heavily pre-treated population. Overall, patients in the study had 3.5 median chemotherapy regimens. 71% of patients were refractory to frontline therapy. Median time from autologous stem cell transplantation to first relapse was 6.7 months.[1]

EFFICACY OF BRENTUXIMAB VEDOTIN

In this trial 75% patients had an objective response by independent review facility. This included 34% patients with complete remission and 40% with partial remission.[1] In addition to this, 22% of patients had stable disease. Assessment of response by the study investigators supported the independent review facility efficacy analysis.[1]

The overall disease control rate, which is the percentage of patients who achieved complete remission, partial remission or had no progression of the disease, was 96%.[1]

TUMOUR SIZE REDUCTION IN 94% PATIENTS

In this phase II trial tumour size reductions were observed in 94% of the patients. Four patients were not included in the analysis; three had no measurable lesions per independent review facility, and one had no post-baseline scans.[1]

KNOWLEDGE CHECK

The objective response rate observed in the trial was

A. 75%
B. 94%
C. 40%
D. 35%

DURATION OF RESPONSE MUCH LONGER WITH COMPLETE REMISSION

Among the 75% of patients who achieved an objective response to brentuximab vedotin, median duration of response was 6.7 months.[1]

The median duration of response among the 34% of patients who achieved complete remission was much longer at 20.5 months.[1]

PROGRESSION FREE SURVIVAL WITH BRENTUXIMAB VEDOTIN: NOTABLY LONGER WITH COMPLETE REMISSION

Progression-free survival (PFS) defined as the time from entry onto the study until lymphoma progression or death as a result of any cause was assessed according to patients' best response to brentuximab vedotin.[1]

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Median PFS in patients who achieved complete remission was 21.7 months. This was notably longer than the PFS observed in patients who did not achieve complete remission. PFS in those with partial remission 5.1 months and 3.5 months in those with stable disease.[1]

PROGRESSION FREE SURVIVAL WITH BRENTUXIMAB VEDOTIN VS. LAST PRIOR SYSTEMIC THERAPY

Fifty-seven of the 102 patients had received systemic therapy at the time of relapse after autologous stem cell transplantation, and before receiving brentuximab vedotin.[1]

A pre-planned analysis was conducted in this patient subgroup to compare progression-free survival after the most recent prior systemic therapy to that with brentuximab vedotin.[1]

The median progression-free survival with the most recent prior systemic therapy was 4.1 months by investigator assessment. When these patients subsequently received brentuximab vedotin, the median progression-free survival was 7.8 months by investigator assessment.[1] Progression-free survival was significantly prolonged with brentuximab vedotin compared with the prior systemic therapy ($P < .001$).

Correlated survival analysis indicated that brentuximab vedotin was associated with a 60% decrease in the risk of death or progression.[1]

PROGRESSION FREE SURVIVAL IN PATIENTS WITH COMPLETE RESPONSE BY SUBSEQUENT TRANSPLANT

At the time of analysis, eight patients who responded to brentuximab vedotin (five patients with complete remission and three patients with partial remission per IRF) had received allogeneic stem cell transplantation immediately after brentuximab vedotin and before any evidence of tumour progression.[1]

The median progression-free survival in patients with CR, who did not receive subsequent allogeneic stem cell transplantation (SCT) was comparable to those who underwent an allogeneic SCT.[1] The median progression-free survival was 21.1 months in the five patients in complete remission who underwent subsequent allogeneic SCT while the median PFS in the 30 patients who achieved complete remission but who did not receive allogeneic SCT was 21.7 months.[1]

KNOWLEDGE CHECK

Which of the following is true about the median progression free survival observed in this trial?

A. Median PFS in patients who achieved complete remission was 21.1 months
B. Median PFS in patients in complete remission who underwent subsequent allogeneic SCT was 21.7 months
C. The median PFS associated with treatment with brentuximab was longer than median PFS associated with the most recent prior systemic therapy
D. All of the above

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OVERALL SURVIVAL

After a 3-year extended follow-up, the median duration of overall survival was 40.5 months. Independent reviewers assessed that 14 patients remain in remission in the same duration of time.[3]

Of the 14 patients in remission 5 received consolidative allogeneic stem cell transplantation following brentuximab vedotin and 9 remain in remission with no additional treatment following brentuximab vedotin.

SAFETY AND TOLERABILITY: PERIPHERAL NEUROPATHY, THE MOST COMMON TREATMENT RELATED ADVERSE EVENT

The most common treatment-related any-grade adverse events were peripheral sensory neuropathy, fatigue, nausea, upper respiratory tract infection, diarrhoea, pyrexia, neutropenia, vomiting, and cough.[3]

Based on data from 2-year follow-up a total of 55% of patients experienced a grade 3 or higher adverse event.[1]

Doses of brentuximab vedotin were delayed due to AEs in 47% of patients. Doses of brentuximab vedotin were prospectively reduced from 1.8 to 1.2 mg/kg in 11 patients, primarily due to peripheral neuropathy.[1]

PERIPHERAL NEUROPATHY: LARGELY REVERSIBLE AND MANAGEABLE WITH DOSE MODIFICATION

Peripheral neuropathy was largely reversible and manageable with dose modification. 9% of the events of peripheral neuropathy were of grade 3 severity and there were no grade 4 events.[3]

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A majority of the patients (80%) had some improvement or resolution of peripheral neuropathy after treatment was completed or discontinued or the dose modified.[1]

Complete resolution of peripheral neuropathy was observed in 50% of patients and the median time to improvement or resolution was 13.2 weeks.[1]

DURATION OF TREATMENT WITH BRENTUXIMAB VEDOTIN

Patients received a median of 9 cycles of treatment with brentuximab vedotin.[1] The number of cycles of treatment with brentuximab vedotin was highest in patients who achieved a complete response.[3]

The recommended duration of treatment with brentuximab vedotin is a minimum of 8 cycles and up to a maximum of 16 cycles administered every 3 weeks.[4]

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EFFICACY OF BRENTUXIMAB VEDOTIN IN PATIENTS WITHOUT PRIOR AUTOLOGOUS SCT

The patients in this study underwent autologous SCT and the results supported the approval of brentuximab vedotin for treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma following ASCT or following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.[4]

However, clinically meaningful responses were observed in phase 1 studies and in named patient programme even with patients without prior ASCT.[4]

Data from patients without prior ASCT and with relapsed or refractory Hodgkins lymphoma who were treated with 1.8 mg/kg of brentuximab vedotin every 3 weeks demonstrated an overall response rate of 54% and a complete response of 22%.[4]

KNOWLEDGE CHECK

The number of cycles of treatment with brentuximab vedotin was highest in patients who achieved a

A. PR
B. CR
C. SD
D. PD

SUMMARY

In the phase II clinical trial 75% of the patients attained objective responses and 34% achieved complete remission. The progression free survival in patients with complete remission was longer than in all other patients and was 21.7 months. The median overall survival for all patients at 3 years follow-up was 40.5 months.

The adverse event profile was manageable and the most common adverse event was peripheral neuropathy which was generally reversible and manageable with dose modification.

Significant clinical response was also observed in patients without prior ASCT as evident from 54% overall response rate and 22% complete response.[4]

Brentuximab vedotin is approved for the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma following autologous stem cell transplant or following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option, and for the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL).[4]

Brentuximab vedotin for treatment of adults with relapsed or refractory sALCL will be discussed in detail in a separate module in the curriculum.

A minimum of 8 cycles and up to a maximum of 16 cycles of 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks is recommended.[4]

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