## MODULE 4

### 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 module will enable understanding of the mechanism of action of brentuximab vedotin and its role in management of relapsed or refractory systemic anaplastic large-cell 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 systemic anaplastic large-cell lymphoma.

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

### INTRODUCTION

Brentuximab vedotin (SGN-35) is an antibody drug conjugate (ADC) which consists of an anti-CD30 antibody linked to an antimicrotubule agent, monomethyl auristatin E (MMAE). The novel linker in brentuximab vedotin is highly stable but is susceptible to degradation by proteolytic enzymes in the lysosomes. This ensures that release of the antimicrotubule agent MMAE occurs only within the target malignant cells and results in programmed death of the malignant cells.[1]

The efficacy of brentuximab vedotin in treating recurrent or relapsed systemic anaplastic large-cell lymphoma, which is an aggressive type of T-cell lymphoma, was studied in a phase II trial. The study included a total of 58 heavily pre-treated patients and the first report was made in 2011 when all patients were followed for a minimum of 6 months and had the disease reassessed after at least 2 cycles of treatment with brentuximab vedotin. This was followed by a later report which recorded the findings from a prolonged 3-year follow-up of the same patients. This report, which had several encouraging findings, was presented at the 55th annual meeting of the American Society of Hematology in December, 2013. [1]

Let us now learn about systemic anaplastic large-cell lymphoma and about the care of patients in the event of recurrence or relapse.

### SYSTEMIC ANAPLASTIC LARGE-CELL LYMPHOMA

Systemic anaplastic large-cell lymphoma (ALCL) is an aggressive subtype of T-cell lymphoma representing approximately 2% to 3% of all lymphoid neoplasms.[1]

With the exception of low intermediate-risk ALK-positive patients, patients with ALCL have a poor prognosis when treated with conventional anthracycline-based front-line chemotherapy.[1]

Approximately 40% to 65% of patients with ALCL develop recurrent disease after front-line therapy. After relapse, ALCL is historically resistant to conventional chemotherapy regimens.[1]

High-dose therapy and autologous hematopoietic stem-cell transplantation (SCT) may result in long-term remission in 30% to 40% of patients, but the benefit is limited to patients with chemotherapy-sensitive disease and patients without advanced age or co-morbidities.[1]

The subset of patients, who have relapsed or refractory ALCL lacks an established standard of care.

Brentuximab vedotin was studied to assess efficacy in patients with relapsed or refractory ALCL.

## PIVOTAL PHASE II TRIAL IN RELAPSED OR REFRACTORY SYSTEMIC ALCL

A phase II trial was conducted with patients with relapsed or refractory ALCL.

The subjects included in the study were individuals with age of 12 years or more who had CD30 positive ALCL which had relapsed or was refractory to at least one prior therapy administered with a curative intent.[1]

These patients had measurable disease, which was defined as having a lesion of 1.5 cm or greater, when assessed by computed tomography and fluorodeoxyglucose-avid disease by positron emission tomography (PET).[1]

Only patients with an Eastern Cooperative Oncology Group performance status of 0 or 1 were included.[1]

The subjects were administered 1.8 mg/kg brentuximab vedotin intravenously over 30 minutes every 21 days for up to 16 cycles and were reassessed at 2, 4, 7, 10, 13, and 16 cycles by an independent reviewer facility (IRF). The patients were then followed-up every 12 weeks.[1]

## BRENTUXIMAB VEDOTIN STUDIED IN A HEAVILY PRE-TREATED ALCL POPULATION

The median age of the subjects was 52 years. ALCL was confirmed in these patients by central pathology in 97 % and 72% were found to have ALK-negative disease.[1]

One crucial baseline feature of the patients included in this trial was the requirement for prior treatment. The individuals in the study were heavily pre-treated.[1]

Many patients received 2 prior chemotherapy regimens as evident from the median number of prior chemotherapy regimens. The number of prior chemotherapy regimens ranged from 1 to 6 and the median number of prior chemotherapy regimens was 2.[1]

45% of the patients had undergone prior radiation therapy and 26% had prior autologus stem-cell transplantation (ASCT).[1]

A majority (62%) were refractory to frontline therapy and half (50%) of the individuals had disease that was refractory to the most recent treatment. 22% had no discernible response to any prior treatment.[1]

Let us now examine the findings of this trial related to the efficacy of brentuximab vedotin in this patient population.

## EFFICACY OF BRENTUXIMAB VEDOTIN

The objective response rate (ORR), defined as the sum of complete responses and partial responses, per independent review was 86%. 59% individuals achieved complete remission and 27% achieved partial remission.[2]

The median duration of objective response (OR) was 13.2 months. In comparison, the median duration in patients who achieved a complete remission was relatively longer at 26.3 months.[2]

The median progression free survival (PFS) for all patients was 14.6 months.[2]

The 3-year follow up also revealed that the median overall survival had not yet been reached and the estimated 3-year survival rate was 63%. Patients who received brentuximab vedotin as part of the study were observed for a median duration of 33.4 months after administration of first cycle.[2]

Please continue with the module to learn about the tumour reductions observed in the trial.

## OVERALL SURVIVAL

Median overall survival was not reached at 33.4 months and the estimated overall survival rate at 3 years was 63%.[2]

## TUMOUR SIZE REDUCTION WITH BRENTUXIMAB VEDOTIN: 97% PATIENTS ACHIEVED TUMOUR REDUCTION

Tumour reductions were seen in 56 of 57 (97%) of the patients and one patient did not have a post-baseline assessment.[1]

## EFFICACY OF BRENTUXIMAB VEDOTIN: SIMILAR EFFICACY IN SUBGROUPS BASED ON BASELINE PROGNOSTIC FACTORS

Differences in individual characteristics of patient subgroups did not affect the response to treatment with brentuximab vedotin.[1]

This was evident from the fact that an analysis of the complete response rate assessed by sub-groups based on baseline prognostic factors revealed that all sub-groups achieved clinically meaningful anti-tumour activity and that the likelihood of achieving CR was similar among the groups analysed.[1]

Possible difference in efficacy of brentuximab was also assessed based on other baseline characteristics such as ALK status, B symptoms and cutaneous lesions. Let us now examine these findings.[1]

## EFFICACY OF BRENTUXIMAB VEDOTIN: ACTIVITY BASED ON ALK STATUS, BASELINE B SYMPTOMS AND MALIGNANT CUTANEOUS LESIONS

Median PFS and duration of response were assessed based on ALK status and no difference was found in median PFS and duration of response between patients with ALK-negative disease and ALK-positive disease.[1]

Other measures of activity such as resolution of B symptoms and malignant cutaneous lesions were assessed[1].

A majority of patients with B symptoms had resolution of the symptoms. All B symptoms resolved after initiation of brentuximab vedotin in 14 (82%) of the 17 patients who had B symptoms at baseline.[1]

Similarly, complete resolution of all malignant cutaneous lesions occurred in all but one of the patients with baseline cutaneous lesions. 14 of 15 patients who had cutaneous lesions at baseline had complete resolution after use of brentuximab vedotin.[1]

## PROGRESSION FREE SURVIVAL WITH BRENTUXIMAB VEDOTIN LONGER THAN PFS WITH MOST RECENT PRIOR THERAPY

Progression-free survival achieved with brentuximab vedotin was compared with that achieved with most recent prior therapy, typically multi-agent chemotherapy or autologous stem cell transplantation.[1]

Data from this study demonstrated that the median PFS as reported by investigator assessment with brentuximab vedotin was 14.3 months. This was longer than the 5.9 month PFS observed with last prior therapy.[1]

## KNOWLEDGE CHECK

Identify the correct statement. (Select the most appropriate option)

A. Median PFS with brentuximab vedotin was longer compared to median PFS with last prior therapy
B. The likelihood of achieving CR was similar among the groups analysed
C. Median overall survival was 33.4 months
D. A and B
E. A, B and C

## OVERALL SURVIVAL BY BEST RESPONSE

After a 3-year extended follow-up, the median OS for patients who obtained a CR had not yet been reached.[2]

The median duration of overall survival varied with the degree of response to brentuximab vedotin. It was observed to be lesser with a lesser degree of response to treatment.[2]

The median OS for patients with partial remission was 9.6 months and for those with stable disease was 10.7 months.[2]

The median duration of overall survival in patients who did not achieve CR was a still shorter 7.7 months.[2]

## OVERALL SURVIVAL AND PROGRESSION-FREE SURVIVAL BY CYCLE 4 PET STATUS

Overall survival and progression free survival were analysed by PET status of the patients at cycle 4 of administration of brentuximab vedotin.[2]

Three patients did not have a PET scan at cycle 4 due to adverse events, 5 did not get a scan due to progressive disease, and the investigator and patient decided against getting a PET scan in 2 different instances. A total of 10 patients did not get a PET scan at cycle 4. [2]

The median OS and PFS in patients with a positive PET scan was 14.6 months and 4.6 months respectively.[2]

The median OS and PFS in patients with a negative PET scan had not yet been reached.[2]

## DURATION OF TREATMENT WITH BRENTUXIMAB VEDOTIN

Patients received a median of 7 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.[2]

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.[3]

Let us now go through a case study that demonstrates the efficacy and safety of brentuximab vedotin in a patient with ALK positive disease.

## CASE STUDY: EFFICACY AND SAFETY OF BRENTUXIMAB VEDOTIN IN A PATIENT WITH ALK POSITIVE DISEASE

The patient was a 42 year old male with ALK positive disease and had received prior chemotherapy and ASCT.[1]

Complete remission was achieved in this patient after four cycles of treatment with brentuximab vedotin.

The patient experienced tumor lysis syndrome after the first dose of brentuximab vedotin; after he recovered from this event, seven additional doses of brentuximab vedotin were administered in the study (eight total doses). The patient received an allogeneic SCT after discontinuing treatment with brentuximab vedotin; 9 months after the last dose in the study, the patient remained in remission.[1]

## KNOWLEDGE CHECK

Complete response was observed in patients who received more cycles of brentuximab vedotin

A. True
B. False

## SAFETY AND TOLERABILITY

The most common adverse events of any grade, occurring in 20% or more of the patients, were peripheral neuropathy, nausea, fatigue, pyrexia, diarrhoea, rash, constipation and neutropenia.[2]

Among these the most common grade 3 events were peripheral neuropathy and neutropenia. The most common grade 4 adverse event was neutropenia.[2]

Other grade 3 or 4 adverse events that occurred in 5% or more of the patients were thrombocytopenia (14%) and anaemia (7%).[2]

Let us continue, to discuss the dose modifications associated with the adverse events.

## ADVERSE EVENTS AND DOSE MODIFICATIONS

Dose delays due to adverse events were required in 40% of patients; however, only 10% of doses were delayed overall.[1]

Seven patients had a dose reduction from 1.8 to 1.2 mg/kg and a total of 14 patients experienced adverse events that led to treatment discontinuation.[1]

The only adverse event that led to treatment discontinuation in more than one patient was peripheral sensory neuropathy (6 patients).[1]

Peripheral neuropathy was the most common adverse event that led to dose delays and dose reduction.[1]

## PERIPHERAL NEUROPATHY: LARGELY REVERSIBLE AND MANAGEABLE WITH DOSE MODIFICATION

The events of peripheral neuropathy observed with treatment with brentuximab vedotin were mostly reversible and were manageable with dose modification.

Thirty one patients (53%) had at least 1 event of peripheral neuropathy which were reported as peripheral sensory neuropathy, paraesthesia, neuralgia, peripheral motor neuropathy, burning sensation, or polyneuropathy.[1]

There were no grade 4 peripheral neuropathy events and the median time to onset of any grade of peripheral neuropathy events was 13.3 weeks.[1]

Of the 31 patients who had peripheral neuropathy, resolution or improvement was observed in 25 (81%) and 15 (48%) had complete resolution.[1]

The median time from onset to resolution or improvement of peripheral neuropathy was 14.1 weeks.[1]

## ADDITIONAL SAFETY FINDINGS OF NOTE

In addition to the safety findings observed with brentuximab vedotin discussed earlier, there were a few other pertinent issues reported.

These include incidences of progressive multifocal leukoencephalopathy, pulmonary toxicity when used along with bleomycin and pancreatitis.

Cases of Progressive multifocal leukoencephalopathy (PML) have been confirmed with brentuximab vedotin used outside clinical studies and a warning outlining the risk of PML has been added to European Union Summary of Product Characteristics (SmPC).[3]

Concomitant administration of brentuximab vedotin and bleomycin is contraindicated due to pulmonary toxicity.[3]

Pancreatitis has been reported in a recent study of previously untreated elderly patients with Hodgkin lymphoma[3] but no wider signals have been seen in clinical data.

## KNOWLEDGE CHECK

The most common grade 3 adverse events observed in the trial were

A. Peripheral neuropathy and thrombocytopenia
B. Thrombocytopenia and anaemia
C. Peripheral neuropathy and neutropenia
D. Thrombocytopenia and neutropenia

## SUMMARY

In conclusion, based on the data from this trial which was the largest prospective trial reported in patients with recurrent or refractory systemic ALCL, a majority of patients responded to treatment with brentuximab vedotin.[1]

Good clinical response as evident from objective responses in 86% of patients and CR in 59% of patients was observed.[2]

A median progression free survival was 14.6 months was observed and the median overall survival had not been reached at 33.4 months.[2]

The clinical benefit of brentuximab was not limited to certain subsets of patients and the PFS and OS observed with treatment was not influenced by ALK status of the patient.[1]

The adverse event profile of brentuximab vedotin was manageable. Peripheral neuropathy was the most common adverse event and was generally reversible and manageable with dose modification.[1]

Brentuximab vedotin is approved for the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma. It is also 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.[3]

Brentuximab vedotin for treatment of adults with relapsed or refractory Hodgkin lymphoma 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.[3]

## REFERENCES


1. Pro B, Advani R, Brice P, Bartlett NL, Rosenblatt JD et al. Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study. *J Clin Oncol*. 2012;30(18):2190-6.
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