OVERVIEW OF CLINICAL PUBLICATIONS OF PIVOTAL TRIALS IN HL AND SALCL

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.

At the end of this module you should be acclimatized with the pivotal phase II trials of brentuximab vedotin in individuals with relapsed or refractory Hodgkin's lymphoma after high-dose chemotherapy and autologous stem-cell transplantation and in patients with relapsed or refractory systemic anaplastic large-cell lymphoma.

You should understand the mechanism of action of brentuximab vedotin and its role in management of relapsed or refractory Hodgkin's Lymphoma and relapsed or refractory systemic anaplastic large-cell lymphoma.

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

Please click next to continue.

RESULTS OF A PIVOTAL PHASE II STUDY OF BRENTUXIMAB VEDOTIN FOR PATIENTS WITH RELAPSED OR REFRACTORY HODGKIN'S LYMPHOMA. YOUNES ET AL. JOURNAL OF CLINICAL ONCOLOGY. JUNE 2012[1]

The following part of the module will discuss the key points of the paper titled 'Results of a Pivotal Phase II Study of Brentuximab Vedotin for Patients with Relapsed or Refractory Hodgkin's Lymphoma.'

INTRODUCTION

The standard of care for patients with relapsed or refractory HL is salvage chemotherapy followed by autologous stem-cell transplantation (auto-SCT) which can induce long term remissions in approximately 50% of patients.

NEED FOR A NEW STANDARD OF CARE

For patients who experience relapse or progressive HL within 1 year after auto-SCT, the prognosis is exceedingly poor, with a median survival time of approximately 1.2 years. This population has no currently available standard of care and represents an urgent unmet medical need

A more recent analysis by Arai et al published in 2013 estimated median post-progression survival for patients who relapse within 12 months after auto-SCT at 0.98 years.

BRENTUXIMAB VEDOTIN – MODE OF ACTION

The malignant Hodgkin's Reed Sternberg cells of classical HL are characterized by the expression of CD30.

Brentuximab vedotin (SGN-35) is an antibody drug conjugate (ADC) comprising an anti-CD30 antibody conjugated by a protease cleavable linker to the potent antimicrotubule agent, monomethyl auristatin E (MMAE). The novel linker used in brentuximab vedotin is highly stable, ensuring that MMAE is released after lysosome entry.

After internalisation and migration to the lysosome, enzymatic cleavage of the ADC occurs to release the cytotoxic agent to the point of action. MMAE is released into the CD30+ cells and results in programmed cell death or apoptosis due to microtubule disruption.

PATIENTS AND METHODS

This phase II trial included subjects with relapsed or refractory HL after high-dose chemotherapy and auto-SCT, histologically documented CD30-positive Hodgkin's Reed-Sternberg cells by central pathology review, and age 12 years or older.

TREATMENT AND ASSESSMENT

1.8 mg/kg of brentuximab vedotin was administered intravenously once every 3 weeks over 30 minutes on an outpatient basis for up to 16 infusions.

Study assessments such as bone marrow biopsy, CT and PET scan were conducted and the best clinical response was determined according to the Revised Response Criteria for Malignant Lymphoma by both investigators and an independent reviewer.

PATIENT CHARACTERISTICS

Seventy-one percent of the patients had primary refractory disease, and 42% had disease that was refractory to the most recent prior therapy.

The median number of prior chemotherapy regimens excluding auto-SCT was 3.5.

Sixty-six percent of patients had received prior radiation therapy, and all 102 patients had undergone auto-SCT of which a majority of patients (71%) had experienced relapse within a year of auto-SCT. The median time to relapse after auto-SCT was 6.7 months.

KNOWLEDGE CHECK

Identify the false statement

A. Seventy-one percent of the patients had primary refractory disease
B. 42% had disease that was refractory to the most recent prior therapy
C. The median number of prior chemotherapy regimens excluding auto-SCT was 3.5
D. All 102 patients had undergone auto-SCT of which a majority of patients (71%) had experienced relapse within a year of auto-SCT
E. None of the above

RESPONSE TO TREATMENT

The objective response rate (ORR) was 75%. 34% of all patients achieved a complete response.

Tumour reductions were observed in 94% of patients.

96% achieved overall disease control which is a measure of complete remission (CR), partial remission and stable disease together.

DURATION OF RESPONSE

The median duration of response was 6.7 months in patients who had an objective response. The median duration of response for patients who achieved a CR was 20.5 months

The estimated 12-month survival was 89%.

The median progression free survival (PFS) for patients who achieved a CR with brentuximab vedotin was 21.7 months, which was notably longer than the median PFS for patients who did not obtain a complete response

COMPARISON OF RESPONSE WITH BRENTUXIMAB VEDOTIN WITH PRIOR THERAPY

A subset of patients (57 of 102 patients) had received a systemic therapy at the time of relapse after auto-SCT. The PFS achieved with the most recent prior systemic therapy and that achieved with brentuximab vedotin was analysed.

The median PFS achieved with the most recent prior systemic therapy was 4.1 months and when these same patients subsequently received brentuximab vedotin, the median PFS was 7.8 months indicating a significant increase with brentuximab vedotin treatment.

KNOWLEDGE CHECK

Median PFS in patients who received brentuximab vedotin compared to the median PFS achieved with the most recent prior systemic therapy was

A. Significantly increased
B. Significantly decreased
C. Not changed
D. Lesser but insignificant

SAFETY

All patients received at least one infusion of brentuximab vedotin. The median number of cycles was 9, the mean number of cycles was 10, and the median relative dose-intensity was 96%.

The most common treatment-related adverse events were peripheral sensory neuropathy, nausea, fatigue, neutropenia, diarrhoea, pyrexia , vomiting, arthralgia, pruritus , myalgia, peripheral motor neuropathy and alopecia

55% of the patients experienced adverse events of grade 3 or higher severity

20 patients had adverse events that led to discontinuation of treatment.

47% patients had delayed doses of brentuximab vedotin due to adverse events. The most common events leading to dose delays were neutropenia and peripheral sensory neuropathy.

Besides peripheral sensory neuropathy, the majority of grade 3 or higher adverse events were laboratory abnormalities including neutropenia, thrombocytopenia, and anaemia.

The median time to onset of peripheral neuropathy events was 12.4 weeks and there were no grade 4 peripheral neuropathy events.

Eighty percent of patients had either resolution or improvement of peripheral neuropathy and complete resolution of all events of peripheral neuropathy occurred in 50% of patients.

The median time to improvement or resolution of peripheral neuropathy was 13.2 weeks.

CONCLUSION

Brentuximab vedotin was administered for a maximum of 16 cycles in this trial; the actual median and mean durations of treatment were 9 and 10 cycles, respectively.

In this pivotal, phase II, trial of brentuximab vedotin monotherapy, 75% of patients achieved an objective response and 34% obtained a CR. Patients had disease that was particularly refractory to prior treatments as evidenced by the fact that 71% of patients did not achieve a CR or had experienced relapse within 3 months of front-line therapy.

Furthermore, these patients had a poor prognosis because the median time to relapse after auto-SCT was only 6.7 months. In this context, the rates of overall response and durable CR are notable for a single-agent therapy after the failure of prior combination chemotherapy and auto-SCT.

These results compare favourably with response rates achieved in the Cancer and Leukemia Group B study of the multiagent regimen of gemcitabine, vinorelbine , and pegylated liposomal doxorubicin in patients with disease relapse after auto-SCT

More than one third of patients achieved a CR with single-agent brentuximab vedotin, and the antitumor activity was obtained without the characteristic toxicity of combination chemotherapy regimens such as gemcitabine, vinorelbine, and pegylated liposomal doxorubicin.

BRENTUXIMAB VEDOTIN (SGN-35) IN PATIENTS WITH RELAPSED OR REFRACTORY SYSTEMIC ANAPLASTIC LARGE-CELL LYMPHOMA: RESULTS OF A PHASE II STUDY. PRO ET AL. JOURNAL OF CLINICAL ONCOLOGY. JUNE 2012.[2]

The following part of the module will discuss the key points of the paper titled ‘Brentuximab vedotin (sgn-35) in Patients with Relapsed or Refractory Systemic Anaplastic Large-cell Lymphoma: Results of a Phase II Study.’

INTRODUCTION

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

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.

NEED FOR A NEW STANDARD OF CARE

Approximately 40% to 65% of patients with ALCL develop recurrent disease after front-line therapy. ALCL is historically resistant to conventional chemotherapy regimens, and lacks an established standard of care.

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.

BRENTUXIMAB VEDOTIN – MODE OF ACTION

Brentuximab vedotin (SGN-35) is an Antibody-drug conjugates (ADC) comprising an anti-CD30 antibody conjugated by a protease cleavable linker to the potent antimicrotubule agent, monomethylauristatin E (MMAE).

Antibody-drug conjugates (ADCs) enable the delivery of a cytotoxic drug to the target malignant cell.

Binding of the ADC to CD30 on the cell surface initiates internalization of the ADC-CD30 complex, which then traffics to the lysosomal compartment, releasing MMAE via proteolytic cleavage

Binding of MMAE to tubulin disrupts the microtubule network, induces cell cycle arrest.

Finally, this results in the death of the CD30-expressing tumour cell by a process of programmed cell death otherwise called apoptosis.

PATIENTS AND METHODS

Subjects enrolled in the trial had a diagnosis of relapsed or refractory systemic ALCL after treatment failure of at least one prior therapy with curative intent.

The most common prior treatment regimen observed was a combination of cyclophosphamide, doxorubicin, vincristine, and prednisone

TREATMENT AND ASSESSMENT

Brentuximab vedotin 1.8 mg/kg was administered intravenously once every 3 weeks over 30 minutes on an outpatient basis for up to 16 total doses.

Both investigators and an independent review facility performed response assessments according to the Revised Response Criteria for Malignant Lymphoma using clinical and imaging assessments.

PATIENT CHARACTERISTICS

Of the total patients with prior therapy 50% of patients experienced relapse and 50% were considered refractory; 62% of patients were primary refractory to front-line treatment.

26% of patients experienced treatment failure with an autologous SCT before study enrolment

KNOWLEDGE CHECK

The most common prior treatment regimen among patients in this study was

A. Cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone (CHOEP)
B. Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)
C. Cyclophosphamide, doxorubicin, vincristine, and dexamethasone
D. Etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin

RESPONSE TO TREATMENT

The objective response rate (ORR) per independent review was 86%. 57% of patients achieved complete response (CR), and 29% achieved partial remission.

Tumour reductions were observed in 97% of patients.

DURATION OF RESPONSE

The median duration of objective response reported in the study was 12.6 months The median duration of response for patients who achieved a CR was 13.2 months.

For the 22 patients who achieved a CR and did not have a subsequent SCT, the median duration of response was 12.6 months, compared with a median of 13.2 months for the six patients who had a subsequent allogenic SCT in CR.

OVERALL SURVIVAL AND PROGRESSION FREE SURVIVAL

At the time of the analysis 18 patients had died and median overall survival (OS) was not reached.

The estimated 12-month survival rate was 70%

Median progression-free survival (PFS) among all patients was 13.3 months.

Among patients with ALK-negative disease, the ORR was 88%, and the CR rate was 52%. These response rates were comparable to those among patients with ALK-positive disease, who had an ORR of 81% and a CR rate of 69%. Median PFS and duration of response were not different between patients with ALK-negative disease and patients with ALK-positive disease.

COMPARISON OF RESPONSE WITH BRENTUXIMAB VEDOTIN WITH PRIOR THERAPY

Median progression free survival (PFS) with brentuximab vedotin was 14.3 months compared with a median PFS of 5.9 months after the most recent prior therapy, including autologous SCT.

The PFS was significantly prolonged with brentuximab vedotin compared with the most recent prior therapy.

SAFETY

All patients enrolled onto this study received at least one dose of brentuximab vedotin. The median number of cycles was 7 and among patients with an objective response, the median number of cycles was 8.

The most common adverse events of any grade, regardless of relationship to brentuximab vedotin, were peripheral sensory neuropathy, nausea, fatigue, pyrexia, diarrhoea, rash, constipation and neutropenia.

Neutropenia, thrombocytopenia, peripheral sensory neuropathy and anaemia were the most common among events of grade 3 or higher severity that occurred in the study.

Adverse events of grade 3 or higher severity were experienced by 60% of the patients

Six deaths occurred within 30 days of the last administration of brentuximab vedotin and none of these deaths were attributed to study drug. Four of the deaths were attributed to disease recurrence

Adverse events led to treatment discontinuation in 14 patients and peripheral sensory neuropathy was the only adverse event that resulted in treatment discontinuation in more than one patient

Doses of brentuximab vedotin were delayed because of adverse events in 40% of patients; however, only 10% of doses were delayed overall. The most common events leading to dose delays were peripheral sensory neuropathy and neutropenia.

The median time to onset of peripheral neuropathy events was 13.3 weeks and the median time to improvement or resolution of peripheral neuropathy was 9.9 weeks.

Resolution or some improvement in peripheral neuropathy was observed in 81% of patients. Complete resolution of all events was achieved in 48% of patients.

KNOWLEDGE CHECK

The most common adverse events of grade 3 or higher severity that occurred in the study were

Peripheral sensory neuropathy, nausea, and fatigue

Pyrexia, diarrhoea, rash, constipation and neutropenia

Neutropenia, thrombocytopenia, peripheral sensory neuropathy and anaemia

Neutropenia, thrombocytopenia, peripheral sensory nausea, and fatigue

CONCLUSIONS

In this trial, which was the largest prospective trial reported in patients with recurrent systemic ALCL, a majority of patients responded to treatment.

Objective responses were observed in 86% of patients and 57% of patients achieved a CR.

Responses generally occurred within 6 weeks of treatment initiation the median duration of response was greater than 1 year.

97% of patients achieved tumour reduction, and disease-related signs and symptoms whenever present at baseline resolved during treatment.

The improvements were independent of ALK status or number of prior therapies, suggesting that responses observed with brentuximab vedotin are not limited to a specific subgroup of patients.

Despite the high percentage of patients with refractory disease, 70% of patients were alive 1 year after the initiation of treatment, with the median overall survival not yet reached.

After achieving remission with brentuximab vedotin in this study, 16 patients received an autologous or allogeneic SCT with the intent of securing a long-term remission.

At the time of this analysis, response durations among these patients were similar, regardless of subsequent transplantation. A sensitivity analysis of PFS of the patients with transplantation and that of the pre-specified analysis revealed that the median PFS was equivalent to the PFS calculated using the pre-specified analysis (13.3 months), indicating that the analyses performed in the study were robust.

The most common adverse events in the study were generally constitutional in nature, with the exception of peripheral sensory neuropathy.

The study results validate a CD30-targeted approach in a disease with uniform antigen expression.

REFERENCES

1. Younes A, Gopal AK, Smith SE, Ansell SM, Rosenblatt JD, et al,. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. *J Clin Oncol*. 2012 Jun 20;30(18):2183-9.
2. 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.