Lorvotuzumab mertansine: antibody-drug-conjugate for CD56+ multiple myeloma

Jesus G. Berdeja

1Multiple Myeloma Research, Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN, USA

1. Abstract
2. Introduction
3. Lorvotuzumab mertansine
   3.1. CD56, the target
   3.2 Characteristics of the antibody-drug-conjugate
4. Preclinical Data
   4.1. Single agent in vitro and in vivo data in multiple myeloma
   4.2. In vitro and in vivo combination data in multiple myeloma
5. Clinical evaluation in multiple myeloma
   5.1. Clinical evaluation of LM single agent
   5.2. Clinical evaluation of LM in combination
6. Toxicity Discussion
7. Clinical Pharmacology
8. Conclusion
9. References

1. ABSTRACT

Lorvotuzumab mertansine (LM) is an ADC composed of an anti CD56 humanized N901 monoclonal antibody conjugated via a stable disulfide linker to the maytansinoid DM1. CD56 is expressed in up to 78% of multiple myelomas. LM displays antitumor activity in preclinical models of multiple myeloma. In a phase I study of MM, the MTD of single-agent LM was 112 mg/m². The dose-limiting toxicities were grade 3 fatigue and grade 3 acute, reversible, renal failure. 2 PRs and 4 MRs were observed at various dose levels starting at 60 mg/m². Building on the single agent experience, a phase II study of LM in combination with lenalidomide and dexamethasone was conducted. The optimal dose of LM was 75 mg/m² in the combination. The ORR was 56.4%. The most common treatment-related AE was peripheral neuropathy (PN), mostly grade 2 or less, with the majority of patients having a grade 1 PN at baseline. Continued evaluation of optimal dosing levels and schedules will be important to better define the utility of this promising treatment.

2. INTRODUCTION

Multiple myeloma (MM) is the second most common hematologic malignancy in the United States with an estimated incidence of 21,700 and an estimated 10,710 deaths in 2012. (1) It is characterized by the proliferation and accumulation of clonal abnormal plasma cells. Treatment options have historically consisted of alkylating agents and steroids. The introduction of high dose chemotherapy, proteasome inhibitors (PIs) and immunomodulating drugs (IMiDs) have significantly expanded the treatment options and translated to deeper remissions and ultimately improved survival.(2) Despite these advances, MM remains an incurable disease with a median survival of 9 months once PIs and IMiDs have failed.(3) Novel therapeutic strategies are sorely needed. One such approach is the use of antibody-based therapy.

The success of monoclonal antibodies such as rituximab and trastuzumab for lymphoma and breast cancer, respectively, has greatly contributed to the ongoing quest for similar success in the treatment of MM. Until
Antibody-drug-conjugate for CD56+ multiple myeloma

recently, the lack of specific and reproducible targets towards malignant plasma cells stalled progress in this disease. Currently, there are several targets that have been identified with directed antibodies to CD38,(4, 5) CS-1,(6, 7) FGFR3,(8) BAFF(9, 10) in clinical development. These monoclonal naked antibodies usually are functional and are dependent on mechanisms of action such as complement activation and/or ADCC to exert their anti-tumor effects.(5, 6)

Monoclonal antibodies can also be exploited to serve as vehicles for on-target delivery of powerful therapy. Antibodies have been conjugated to radioactive isotopes and cytotoxic agents with various levels of success in different tumor types.(11-16) Many of the early challenges were multifactorial including the specificity of targets and the limitations imposed by the pharmacokinetic and pharmacodynamics properties of monoclonal antibodies and their conjugates.(11, 17) With improvements in linker technology and development of more potent drug conjugates, in particular the maytansine derivatives (17, 18) the list of clinically active antibody-drug-conjugates (ADC) has greatly expanded.(19, 20) Lorvotuzumab mertansine encompasses these advances in ADC technology and is the first of its kind in the treatment of CD56-positive MM.

3. LORVOTUZUMAB MERTANSINE

3.1. CD56, The Target

CD56 is a membrane glycoprotein, also known as neural cell adhesion molecule (N-CAM), that is expressed on neural tissues and essentially all human natural killer (NK) cells and a subset of cytotoxic T cells.(21) Its function has yet to be fully defined. CD56 is also expressed in various malignant tissues including small cell lung cancer, neuroblastoma, ovarian cancer and other neuroendocrine tumors.(22, 23) Interestingly, CD56 is not expressed in benign plasma cells and only mixed expression in the plasma cells of patients with monoclonal gammopathy of undetermined significance (MGUS).(24, 25) Conversely, CD56 is strongly expressed in up to 78% of MM. Although its function in MM cells is unknown, there are reports of CD56 positivity correlating with increased bone disease and loss of CD56 upon progression to plasma cell leukemia.(26, 27)

3.2. Characteristics of the antibody-drug-conjugate

Lorvotuzumab mertansine (IMGN901, BB-10901, huN901-DM1; ImmunoGen, Inc., Waltham, MA, USA) is an ADC composed of the cytotoxic maytansinoid derivative, DM1, conjugated via a stable disulfide linker to the humanized N901 monoclonal antibody (lorvotuzumab, huN901), which binds CD56 with high affinity. A schematic representation is shown in Figure 1. Once bound to CD56 on the surface of the target cell the conjugate is internalized, the linker is cleaved, DM1 is released which in turn inhibits tubulin polymerization and results in cell death. (See Figure 2) Maytansine is a natural product, originally derived from the Ethiopian shrub *Maytenus serrata*. Maytansine inhibits tubulin polymerization, and is approximately 200-1,000 fold more cytotoxic than the *Vinca* alkaloids.(26) Maytansine is clinically active but its narrow therapeutic window precluded further clinical development. Conjugation to an antibody and intracellular delivery could take advantage of the cytotoxic potency and expand the therapeutic window leading to greater tumor cell death with less overall toxicity. The maytansine derivative DM1 was developed specifically for use in ADCs.(17, 29)

4. PRECLINICAL DATA

4.1. Single agent *in vitro* and *in vivo* data in multiple myeloma

Tassone et al. were able to show that LM selectively inhibits growth of CD56-positive MM cell lines.
Antibody-drug-conjugate for CD56+ multiple myeloma

Figure 2. Lorvotuzumab mertansine (LM) mechanism of action. LM binds with high affinity to CD56 on the surface of tumor cells; is internalized • Inside cell, DM1 is released via linker cleavage • DM1 disrupts tubulin polymerization and microtubule assembly, resulting in tumor cell death. Reproduced with permission from ImmunoGen, Inc., Waltham, MA.

without effects on CD56-negative MM cell lines.(26) Interestingly, the level of growth inhibition was independent of the level of expression of CD56 on the surface of the cells. Furthermore, the unconjugated lorvotuzumab antibody did not demonstrate any inhibitory effects whereas DM1 was inhibitory to both CD56-positive and CD56-negative cell lines. This nicely demonstrates the ability of the ADC to specifically deliver the cytotoxic agent to the cells expressing CD56 and sparing the cells that lack that expression.(26)

Using a human CD56-positive MM xenograft model in severe combined immunodeficient (SCID) mice, LM was tested in both a minimal disease state and a bulky disease state. Mice were treated with LM, a saline placebo, unconjugated lorvotuzumab antibody or a control ADC that did not target CD56. Neither lorvotuzumab nor the control ADC showed any growth inhibition or survival benefit over placebo. Conversely, LM treatment led to a significant reduction in serum paraprotein, inhibition of tumor growth and an improved overall survival in the minimal disease state. Likewise, in the mice with bulky tumors, LM resulted in significant delayed tumor growth to complete inhibition of tumor growth with increasing doses and an improved overall survival at all doses tested.(26)

4.2. In vitro and in vivo combination data in multiple myeloma

Using cultured human CD56-positive MM cell lines LM has been shown to have additive cytotoxic effects when combined with thalidomide and dexamethasone, and to have additive to synergistic effects when combined with melphalan.(30) Interestingly, combinations with bortezomib were found to be slightly antagonistic in vitro, but additive to synergistic in vivo.(30, 31) In combination with lenalidomide and lenalidomide plus dexamethasone, highly synergistic cytotoxic effects were seen.(31)

Using MM xenografts in SCID mice, the additive and synergistic effects were able to be confirmed in vivo. Although LM treatment resulted in tumor regression at all doses tested, only one mouse had complete regression.(30)
Antibody-drug-conjugate for CD56\(^+\) multiple myeloma

Table 1. Dose escalation for LM, lenalidomide, dexamethasone study

<table>
<thead>
<tr>
<th>Disposition</th>
<th>Assigned</th>
<th>Dose Level</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>75 mg/m(^2) n (%)</td>
<td>90 mg/m(^2) n (%)</td>
<td>112 mg/m(^2) n (%)</td>
</tr>
<tr>
<td>Enrolled</td>
<td>34 (100.0)</td>
<td>4 (100.0)</td>
<td>6 (100.0)</td>
</tr>
<tr>
<td>Dose Escalation</td>
<td>11 (32.4)</td>
<td>4 (100.0)</td>
<td>6 (100.0)</td>
</tr>
<tr>
<td>Dose Expansion</td>
<td>23 (67.6)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>On Study</td>
<td>10 (29.4)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Date of data cut-off: 16 November 2012 (represents both monitored and unmonitored data; data review ongoing). Reproduced with permission from, (39).

When LM was given in combination with bortezomib or melphalan, all mice achieved complete tumor regressions, responses well above those seen with either single agent.(30) Furthermore, when using the same model, the combination of LM, lenalidomide and dexamethasone demonstrated greater-than-additive anti-tumor effects compared to treatment with either agent alone.(32)

5. CLINICAL EVALUATION IN MULTIPLE MYELOMA

5.1. Clinical evaluation of LM single agent

Given the promising preclinical data, LM was initially evaluated as monotherapy in a phase I study in patients with relapsed and relapsed/refractory CD56-positive MM. The primary objective of the study was to determine the maximum tolerated dose (MTD), to determine pharmacokinetics (PK) and to assess preliminary signal of single agent activity.(33) LM was given intravenously (IV) at doses ranging from 40 to 140 mg/m\(^2\)/week for two consecutive weeks with cycles repeating every three weeks. During the dose escalation phase of the study, patients were enrolled into each dose level in cohorts of three, with a dose-limiting toxicity (DLT) triggering cohort expansion. Once the MTD was determined, an expansion cohort at that dose level was open to further characterize the safety and efficacy of LM. As of the most recent presentation, 37 patients had been treated on study.(34) The patients were very heavily pretreated with a median number of 6 prior MM therapies. Two patients experienced DLTs of grade 3 fatigue and grade 3 acute, reversible, renal failure at a dose of 140 mg/m\(^2\), and the MTD was declared at 112 mg/m\(^2\). A total of 19 patients were treated at the MTD.

The most common adverse events (AE) were fatigue, peripheral neuropathy (PN) and headache, while the most common abnormal laboratory findings included increased aspartate aminotransferase and increased uric acid. Six patients experienced drug-related grade 3 AEs: fatigue and renal failure (one patient) and one patient each with weakness, absence of deep tendon reflexes, myalgia, peripheral sensory neuropathy and elevated lipase. Only the renal failure met severe adverse event (SAE) criteria. There were no grade 4 drug-related AEs were reported. There was no evidence of infusion-related toxicity, hypersensitivity reactions or development of humoral response to either the lorvotuzumab antibody component (HAHA) or the DM1 component (HADA).(34)

Single agent clinical activity was observed at various dose levels starting at 60mg/m\(^2\) in this very refractory CD56-positive MM population.(34) Fifteen of 37 patients (41\%) showed clinical benefit (≥ stable disease for at least 3 months), including 2 partial responses (PR) and 4 minor responses (MR) using the European Bone Marrow Transplant (EBMT) Criteria.(35) In those patients who achieved an objective response, durability of at least 3 months, and up to 20 months was observed. (35)

5.2. Clinical evaluation of LM in combination

Building on the single agent experience and the promising in vitro and in vivo combination studies, a phase I study of LM in combination with lenalidomide and dexamethasone was initiated. In the dose escalation phase of the study patients with CD56-positive relapsed or relapsed/refractory MM with at least one prior treatment and no upper limit on number of prior treatments were included. Patients who had previously been treated or were refractory to lenalidomide were eligible for the dose-escalation portion of the study. Patients who enrolled in the dose expansion cohort may have received lenalidomide previously, but must have achieved stable disease or better in response to prior lenalidomide therapy, and must have been > 6 months from their last full dose of lenalidomide. The majority of patients (72.7\%) had grade 1 peripheral neuropathy (PN) at study entry. Treatment consisted of 28-day cycles of lenalidomide 25 mg orally daily on days 1-21, dexamethasone 40 mg orally on days 1, 8, 15, 22, and escalating doses of LM IV on days 1, 8, 15. A total of three dose levels of LM were evaluated, 75 mg/m\(^2\), 90 mg/m\(^2\) and 112 mg/m\(^2\). An overview of the dose escalation details are depicted in Table 1. Although cycle 1 DLTs were not observed during the portion of this phase I study, grade 3 PN was observed in subsequent cycles of treatment and required dose reductions at dose levels of 90 mg/m\(^2\) and 112 mg/m\(^2\). Based on this clinical observation and because clinical activity was seen at all dose levels, a dose of 75 mg/m\(^2\) was ascertained to be the optimal dose for additional exploration in the expansion cohort.(36)

A total of 44 patients (34 at the recommended expansion dose of 75 mg/m\(^2\)) were treated on study. The median number of prior treatments was 2 with 45% patients having had ≥ 3 prior treatments (91\% had prior bortezomib, 75\% had prior IMiDs, 59\% had prior lenalidomide, 36\% were refractory to their last treatment). Of the 44 patients enrolled, 39 were evaluable for response. Using the International Myeloma Working Group Criteria (IMWG), (37, 38) the overall response (OR) (defined as ≥PR) was 56.4\% with a clinical response (defined as ≥MR) of 64.1\% (1 stringent complete response (sCR), 11 very good partial remissions (VGPR), 10 PRs, 3 MR, 12 SD). In the lenalidomide naïve group, lenalidomide exposed/refractory,
Antibody-drug-conjugate for CD56+ multiple myeloma

Table 2. Best responses on study, all dose levels, n(%)\(^1\)

<table>
<thead>
<tr>
<th></th>
<th>Evaluable Patients(^2)</th>
<th>Lenalidomide Naïve</th>
<th>Received Prior Len Refractory</th>
<th>Lenalidomide (Including Relapsed &amp; Refractory) to Last Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total N</td>
<td>39 (100.0)</td>
<td>16 (41.0)</td>
<td>23 (58.9)</td>
<td>12 (30.8)</td>
</tr>
<tr>
<td>Overall Response (&gt;PR)</td>
<td>22 (56.4)</td>
<td>14 (87.5)</td>
<td>8 (34.8)</td>
<td>6 (50.0)</td>
</tr>
<tr>
<td>Clinical Response (&gt;MR)</td>
<td>25 (64.1)</td>
<td>14 (87.5)</td>
<td>11 (47.8)</td>
<td>6 (50.0)</td>
</tr>
</tbody>
</table>

Abbreviations: PR, partial response; MR, minimal response. \(^1\)Date of data cut-off: 16 November 2012 (represents both monitored and unmonitored data; data review ongoing), \(^2\)Response evaluable patients received at least one dose of drug and 1 post-dose tumor assessment. \(^3\)Relapsed and refractory myeloma: disease that is nonresponsive while on salvage therapy, or progresses within 60 days of last therapy in patients who have achieved ≥ minimal response previously. Reproduced with permission from, (39).

Table 3. Most common (≥ 15%) AEs related to study regimen (LM/len/dex) at 75 mg/m\(^2\)

<table>
<thead>
<tr>
<th>N = 34</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral Neuropathy</td>
<td>19 (55.9)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14 (41.2)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>11 (32.4)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>11 (32.4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>10 (29.4)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9 (26.3)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>8 (23.5)</td>
</tr>
<tr>
<td>Muscle Spasms</td>
<td>7 (20.6)</td>
</tr>
<tr>
<td>Anemia</td>
<td>6 (17.6)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>6 (17.6)</td>
</tr>
</tbody>
</table>

Abbreviations: AEs, adverse events; LM, lorvotuzumab mertansine; len, lenalidomide; dex, dexamethasone Date of data cut-off: 16 November 2012 (represents both monitored and unmonitored data; data review ongoing). Reproduced with permission from, (39).

The most common AEs seen in ≥15% of patients that could be attributed to any of the study drugs are listed on Table 3. The most common treatment-related AEs, listed in descending order, were PN, fatigue, neutropenia, thrombocytopenia, nausea and diarrhea. Most reports of PN were grade 2 or less with the majority of patients having a grade 1 PN at baseline. Nonetheless, PN was the single most common cause for dose reductions.

6. TOXICITY DISCUSSION

The expression of CD56 on normal human peripheral nerves, cardiac muscle, various neuroendocrine cells and NK cells may help explain some of the toxicities observed in the clinical trials. In preclinical studies in Cynomolgus monkeys, who share similar CD56 expression with humans, PN was seen at the highest doses tested. (ImmunoGen, Waltham, MA) Clinically, the most salient toxicity has been peripheral neuropathy both in the single agent and in combination with lenalidomide and dexamethasone. Given the preclinical toxicity data perhaps this should not be unexpected. Having said that, the PN seen in the MM studies seems more pronounced than that seen in solid tumors.(40) Most relapsed MM patients have baseline PN as a result of prior treatments or the disease itself, thus PN in this population may be more difficult to assess. Furthermore, other non CD56-directed ADCs using similar tubulin-disrupting cytotoxins have reported the emergence of PN as an important side effect.(19, 20) This would argue that perhaps the PN is more of a class effect in ADCs that utilize tubulin-acting cytotoxins due to low systemic levels of cytotoxin (or cytotoxin metabolites) released as a result of cellular catabolism following target-mediated or non target-mediated uptake mechanisms.(41) Further investigation as to the frequency of dosing and in less heavily pretreated MM populations would help define this particular toxicity.

7. CLINICAL PHARMACOLOGY

PK analyses in the single agent phase I study revealed an approximate linear relationship between dosing and observed maximal serum concentration. The elimination half-life of the ADC ranged between 16-24 hours. Interestingly, the half-life of the lorvotuzumab antibody component and the intact ADC are similar suggesting that clearance of this particular ADC is driven by antigen-dependent process such as uptake by CD56-positive NK cells or CD56-positive tumor cells. Targeting of the ADC to myeloma cells was confirmed by immunohistochemical analysis of bone marrow tissue obtained one day post treatment.(33, 42)

The PK parameters of LM for patients treated in combination with lenalidomide and dexamethasone in the expansion cohort (LM 75 mg/m\(^2\)) were generally similar to those observed with the single agent at this same dose.(39) Furthermore, the PK parameters of lenalidomide and dexamethasone in combination with LM at 75 mg/m\(^2\) were similar to published reports of lenalidomide and dexamethasone.(43-45) These results suggest no drug-drug interaction with this combination.
Antibody-drug-conjugate for CD56+ multiple myeloma

8. CONCLUSION

Until recently, clinically effective antibody-based therapy has eluded MM. The lack of bulky tumor masses in the majority of patients with MM should theoretically allow for greater target exposure thus making MM an ideal cancer indication for antibody-based approaches. LM is the first ADC shown to have clinical activity in CD56-positive relapsed/refractory MM. The initial studies with single agent LM and in combination with lenalidomide and dexamethasone have reported significant objective responses and clinically relevant stable disease in heavily pretreated populations. In vitro studies clearly show that CD56 expression is imperative for on target delivery of the cytotoxic drug, though the level of expression required is not clear.(26) Why some patients respond while others do not remains an active area of investigation. One can postulate that some mechanisms of resistance to ADCs may involve down regulation of the target, increased drug efflux, and downstream anti-apoptotic effects, among others.(46) To date, there is no clear evidence that LM leads to down regulation or loss of CD56 expression.

LM is generally very well tolerated. Similar to other ADCs containing tubulin-disrupting agents, PN has emerged as an important side effect. Continued evaluation of optimal dosing levels and schedules and treatment of patients earlier in the course of the disease prior to development of progressive neuropathy will be important to better help define the utility of this promising treatment. Finally, its favorable pharmacokinetics and minimal overlapping toxicities make LM ideal for continued exploration in combination studies.

9. REFERENCES


5. J. Endell, R. Boxhammer, C. Wurzenberger, D. Ness and S. Steidl: The Activity of MOR202, a Fully Human Anti-CD38 Antibody in Patients with Multiple Myeloma - Data From a Dose-Escalation Phase I/II Study. ASH Annual Meeting Abstracts, 120(21), 73-2012


8. CONCLUSION

Until recently, clinically effective antibody-based therapy has eluded MM. The lack of bulky tumor masses in the majority of patients with MM should theoretically allow for greater target exposure thus making MM an ideal cancer indication for antibody-based approaches. LM is the first ADC shown to have clinical activity in CD56-positive relapsed/refractory MM. The initial studies with single agent LM and in combination with lenalidomide and dexamethasone have reported significant objective responses and clinically relevant stable disease in heavily pretreated populations. In vitro studies clearly show that CD56 expression is imperative for on target delivery of the cytotoxic drug, though the level of expression required is not clear.(26) Why some patients respond while others do not remains an active area of investigation. One can postulate that some mechanisms of resistance to ADCs may involve down regulation of the target, increased drug efflux, and downstream anti-apoptotic effects, among others.(46) To date, there is no clear evidence that LM leads to down regulation or loss of CD56 expression.

LM is generally very well tolerated. Similar to other ADCs containing tubulin-disrupting agents, PN has emerged as an important side effect. Continued evaluation of optimal dosing levels and schedules and treatment of patients earlier in the course of the disease prior to development of progressive neuropathy will be important to better help define the utility of this promising treatment. Finally, its favorable pharmacokinetics and minimal overlapping toxicities make LM ideal for continued exploration in combination studies.

9. REFERENCES


Antibody-drug-conjugate for CD56+ multiple myeloma


Antibody-drug-conjugate for CD56+ multiple myeloma

Key Words: Antibody-drug-conjugate, CD56, Multiple myeloma, Lorvotuzumab mertansine, DM1, Review

Send correspondence to: Jesus G. Berdeja, Director of Multiple Myeloma Research, Sarah Cannon Center for Blood Cancer, 250 25th Avenue N, Suite 412, Nashville, TN, 37203, Tel: 615-986-7602, Fax: 615-986-7645, E-mail: jberdeja@tnonc.com