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Daratumumab for the treatment of AL Amyloidosis

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Abstract

Autologous stem cell transplantation (ASCT) has been used as treatment for immunoglobulin light chain (AL) amyloidosis for over two decades with improving outcomes; however the majority of patients are not candidates for this therapy at diagnosis. Novel agents such as immunomodulatory drugs, proteasome inhibitors and immunotherapy with monoclonal antibodies targeting CD38 have been adopted from the multiple myeloma sphere with encouraging results. Herein we discuss the role of daratumumab, a monoclonal antibody to CD38, in the treatment of AL amyloidosis. We focus on its mechanism of action, tolerability and the current published data on its use in AL amyloidosis. Early data from phase I and phase II studies show that daratumumab is tolerated well in this population and induces rapid and deep responses. Phase III trials are currently accruing and we envision daratumumab becoming a key component in the treatment of AL amyloidosis in the future.

Keywords

Daratumumab; AL amyloidosis; monoclonal antibody; CD38; immunotherapy

Introduction

Immunoglobulin light chain (AL) amyloidosis is a clonal disorder of plasma cells or less commonly B cells that produce misfolded immunoglobulin light chain that deposits in tissues of a variety of organs causing organ dysfunction.(1, 2) The incidence is approximate 6–10 cases per million per year.(3) Commonly affected organs include the heart (75%), kidney (65%), liver (15%), soft tissues (15%), peripheral and/or autonomic nerves (10%) and the gastrointestinal tract (5%).(4) The diagnosis is established by demonstration of amyloid deposition on tissue biopsy of the affected organ; the amyloid deposits show Congo red positivity with apple-green birefringence under polarized light. Mass spectrometry should be used to confirm the amyloid precursor protein type as AL.(5) When not available, immunohistochemical methods may be used to confirm subtype of amyloidosis.(6, 7)The prognosis of AL amyloidosis is heavily dependent on degree of organ involvement, in particular cardiac involvement, and median overall survival ranges from as short as six months to over five years.(8)

Given an abnormal plasma cell clone is central to the development of AL amyloidosis, treatment has traditionally focused on suppressing production of the immunoglobulin light chain and has been extrapolated from the experience in multiple myeloma. Agents such as melphalan in combination with prednisone were initially used and although the regimen was well tolerated, efficacy was only modest.(9) High dose therapy with stem cell rescue showed promising results in myeloma, prompting investigation of this therapy in AL Amyloidosis. Significant safety concerns with treatment-related mortality (TRM) reports ranging from 13–43% were raised in the initial clinical trials exploring autologous stem cell transplantation (ASCT) in AL amyloidosis.(10–12) Over time selection criteria for eligibility for stem cell transplant evolved with improvements in TRM (down to < 5%) and long term survivors, with some reports showing a 43% survival rate at 10 years.(13–15) Despite these improvements, utility of ASCT in AL amyloidosis is limited by patient eligibility, with only 20–25% of patients presenting to our institution being eligible for this therapy. The major contraindication is typically age, advanced cardiac failure or multi-organ involvement.

Patients ineligible for transplant, particular those with cardiac involvement have poor outcomes, with median overall survival reported at less than one year and represent an area of unmet need in the treatment of AL amyloidosis.(16) Novel therapies including proteasome inhibitors and immunomodulatory drugs (IMiDs) have revolutionized therapy for multiple myeloma with improved response rates and survival(17). Both agents have been studied in clinical trials for patients with AL amyloidosis with promising results.(18–22) Upfront therapy with a combination of Bortezomib, cyclophosphamide and dexamethasone in a large cohort of patients showed a hematologic response rate of 62% with cardiac and renal response rates of 17% and 25% respectively.(19) In addition, induction therapy with this regimen in transplant ineligible patients has been shown to improve patient status to allow consideration for ASCT.(21) The combination of lenalidomide, cyclophosphamide and dexamethasone was studied in a phase II study of transplant ineligible patients, showing a hematologic response rate of 46%, organ response rate of 46% and median progression free and overall survival not reached after a median follow up of 24 months.(23) While these results are encouraging there remain a significant proportion of patients that do not respond to these agents and alternative options are needed.

1. Daratumumab

Daratumumab is a first-in-class human IgG1k monoclonal antibody (mAb) that binds with high affinity to a unique epitope of CD38, an antigen that is highly and uniformly expressed on the surface of multiple myeloma cells.(24, 25) Daratumumab induces myeloma cell death via a variety of mechanisms including complement dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, antibody-dependent cellular phagocytosis and direct cellular apoptosis, Figure 1.(25) Trials of daratumumab in combination with other novel agents in relapsed myeloma have shown dramatic response rates and improved progression free survival.(26, 27) Two features of daratumumab from the trials thus far stand out; firstly the depth of response achieved has been particularly impressive, with the POLLUX study showing a minimal residual disease(MRD) negativity rate of 22.4% when daratumumab is combined with lenalidomide and dexamethasone compared to 4.6% in the lenalidomide and dexamethasone alone arm, and secondly the drug is extremely well tolerated with the major

drug specific adverse effect being manageable infusion related reactions that almost entirely occur during the first cycle.(27) Given the abnormal plasma cell clone in AL amyloidosis also expresses CD38; it is only natural to consider daratumumab as a therapeutic option for this disorder. In addition the need to achieve deeper responses to completely turn off production of the amyloidogenic light chain in AL amyloidosis makes, daratumumab an attractive option to consider.

2. Daratumumab for AL Amyloidosis

The use of daratumumab for AL amyloidosis is evolving, and despite there being no phase three randomized trials, several reports have confirmed its efficacy with a number of clinical trials on the horizon.

Initial reports of its efficacy in this group of patients were published by Sher et al.(28) They reported two cases of AL amyloidosis, the first with cardiac and hepatic involvement and the second with renal involvement, that were treated with daratumumab. Both patients had previously been exposed and refractory to proteasome inhibitors (Bortezomib and Carfilzomib), lenalidomide and an autologous stem cell transplant. Both patients achieved a hematologic complete remission with normalization of the serum light chains. These cases highlighted a number of important points; firstly that daratumumab is active in this patient cohort despite multiple previous therapies, secondly that deep hematologic responses are achievable to help markedly reduce production of the amyloidogenic light chain, and thirdly that daratumumab can be safely administered to patients with AL amyloidosis. Both patients tolerated treatment well with only a mild infusion reaction reported in the second patient.

This initial report of efficacy was followed by a report in a larger cohort of AL amyloidosis patients treated with daratumumab by Kaufman and colleagues at Stanford University.(29) They conducted a retrospective review of all patients with AL amyloidosis treated with daratumumab over a 12 month period. Their cohort of 25 patients had a median number of lines of prior therapy of 3 and had all previously been exposed to proteasome inhibitors with 72% having also received IMiDs. Only 4 patients had undergone ASCT; likely to reflect the degree of organ involvement and comorbidity in the group. 60% of patients were refractory to their last line of therapy. Cardiac and renal involvement was present in 72% and 68% of patients respectively. Daratumumab was administered at the standard schedule as used in multiple myeloma, intravenously at a dose of 16mg/kg weekly for 8 weeks, followed by every other week for 8 doses, and then every 4weeks thereafter. The authors note that patients were admitted to hospital for the first infusion which was split over two consecutive days.

The responses were rapid and impressive. The hematologic response rate was 76% with 36% achieving a complete response (CR) and 24% achieving a very good partial response (VGPR) with a median time to deepest response of 1 month. Daratumumab was well tolerated with the most common adverse event reported being grade 1–2 infusion related reactions, occurring in 60% of patients. Importantly, patients with cardiac involvement tolerated therapy well without evidence of decompensation related to infusion of daratumumab. The median follow-up at the time of publication was reported to be 7 months;

as such important questions regarding duration of response, progression free survival and organ response remain unanswered.

Prospective data is now starting to emerge regarding the safety and efficacy of daratumumab in AL amyloidosis. Preliminary results from two prospective Phase II studies were initially presented at the annual meeting for the American Society of Hematology in 2017 and at the International Symposium on Amyloidosis meeting in 2018. Sanchowala et al presented preliminary results of their phase II study (NCT02841033) in a cohort of 12 patients with relapsed AL amyloidosis, prospectively enrolled to receive daratumumab.(30) Their primary endpoint was safety and tolerability with regards to infusion reactions with secondary endpoints including hematologic response, organ response and time to next therapy. They employed a comprehensive pre-infusion medication regimen that included acetaminophen, diphenhydramine, loratidine, famotidine, montelukast, methylprednisolone and the addition of ondansetron after grade 1 nausea and vomiting was observed in the first two patients. Patients had to have at least 2 prior lines of therapy with 75% having undergone previous ASCT. Daratumumab was administered according to the standard regimen used in myeloma. No patients experienced grade 3 or 4 infusion reactions. After introduction of ondansetron no further episodes of nausea or vomiting were reported during the infusion. Patients were not hospitalized for infusion reactions and the median infusion time for first and second daratumumab doses were 6.95 and 4.45 hours respectively. Interestingly they report rapid reduction in serum free light chain levels with 10 out of 12 patients achieving levels consistent with a VGPR after a single infusion of daratumumab. The data are not yet mature to assess the durability of these responses. Of note however, were the 5 patients with renal involvement available for assessment after 6 months; 4 had significant organ response with a >30% reduction in urine protein excretion.

The second study presented was a multi-center phase II study across France and Italy that had enrolled 35 out of a target accrual of 40 patients. These were relapsed or refractory patients with a median age of 69 and median prior therapies of 3. A significant number of patients had previous exposure to IMiDs (51%) and bortezomib (94%). They reported grade I or II infusion reactions in 10 patients during the first infusion. After at least one cycle of therapy they report an overall response rate of 59% with 44% of patients achieving at least a VGPR. The study is ongoing (NCT02816476) and data regarding response after longer durations of therapy and organ responses are yet to mature.(31)

Furthermore two larger retrospective studies were also reported at the International Symposium on Amyloidosis meeting March 2018. The first by Kimmich et al from Heidelberg reported efficacy of daratumumab monotherapy in 48 previously treated (median 3 prior lines of therapy) patients with AL amyloidosis.(32) Patients received a median of 8 infusions of daratumumab with 32 (65%) patients achieving a hematologic response (5 CR, 19 VGPR and 8 PR). With a median follow up of 7.9 months median progression free survival (PFS) was 9.5 months and median overall survival (OS) not reached. Mild upper respiratory tract infections were reported in 6 patients. Nine patients with advanced cardiac amyloidosis had died, 7 from cardiac events and 2 from infections. Respiratory infections in a population with advanced cardiac amyloidosis may cause significant decompensation. The

incidence of this adverse event will need to be closely monitored in ongoing trials of daratumumab in this patient population.

The second report was data from Mayo Clinic with daratumumab based therapies in 41 patients (20 receiving monotherapy and 21 receiving combination therapy) with relapsed or refractory AL amyloidosis.(33) After a median follow up time of 7.5 months overall hematologic response rate in 30 evaluable patients was 80%. Organ involvement at baseline included cardiac in 24 (58%), renal in 19 (46%) and hepatic in 3 (7%) patients. Cardiac response was seen in 8 (33%) and renal response in 6 (32%) patients, with no patient achieving a hepatic response. Organ responses need to be interpreted in the context of a short follow up period. The median PFS was 16.2 months with median duration of response not reached. Median OS for the cohort from initiation of daratumumab based therapy was not reached. Infusion reactions were seen in 24% of patients and at time of last follow up 31 patients remained on daratumumab based therapy. Both these studies show encouraging results and need to be interpreted in the context of a pretreated population of patients.

In addition to these retrospective studies, the first report of daratumumab as first line therapy in AL amyloidosis was also presented at the meeting. Two patients with histologically confirmed AL amyloidosis and advanced Mayo cardiac stage (Stage III and Stage IV respectively) were treated with daratumumab monotherapy.(34) Both tolerated the therapy well without serious adverse events and achieved normal light chain levels within one cycle of therapy. This data highlights the potential for daratumumab therapy in a group of patients that traditionally have a poor prognosis and often do not tolerate conventional therapy well.

These early phase studies have provided encouraging data regarding the safety and tolerability of daratumumab in AL amyloidosis. In addition, there is a rapid response, in some cases patients achieving a CR after a single infusion of daratumumab. This has provided the rationale for exploring daratumumab earlier in the disease course of AL amyloidosis and there is currently an actively recruiting phase III trial comparing cyclophosphamide, bortezomib and dexamethasone with or without daratumumab in the treatment of newly diagnosed AL amyloidosis ([NCT03201965](#)).

3. Daratumumab Practical Points

Response assessment—One of the issues that have emerged from experience with daratumumab in myeloma is its effect on response assessment. Response assessment in multiple myeloma relies on serological assessment with serum protein electrophoresis (SPEP) and immunofixation electrophoresis (IFE).(35) As a human IgGκ immunoglobulin, daratumumab may be detected by IFE and can thus be misinterpreted as a myeloma-associated M-protein, thereby interfering with the response criteria.(36) Response criteria in AL amyloidosis although more reliant on the immunoglobulin free light chain assay, nevertheless requires both SPEP and IFE assessment, particularly in establishing CR.(37) A daratumumab specific IFE reflex assay (DIRA) has been developed and can be utilized to overcome this interference and allow for accurate response assessment.(38) Preclinical data suggests this is less of an issue with the serum free light chain assay.(39) The use of mass spectrometric analysis of serum can easily differentiate a therapeutic mAb such as daratumumab from a myeloma clone and will become important as use of immunotherapies

increases.(40) Another aspect of response and disease assessment clinicians should be aware of is enumeration of plasma cells by flow cytometry. Daratumumab binding on to CD38 on the surface of plasma cells may prevent their detection by flow cytometry, where CD38 is a critical marker for assessment of presence and enumeration of plasma cells.

Pretransfusion Testing—CD38 is weakly expressed on red blood cells (RBCs) and patients receiving daratumumab show false-positive reactivity on indirect antiglobulin tests (IAT) used for the detection of irregular blood group antibodies.(41) This can complicate blood transfusion and compatibility testing, particularly in a population that may have marrow suppression and need for blood products. If daratumumab is adopted for initial myeloma therapy and patients receive myeloablative consolidation this problem will be very common. The transfusion laboratory may consider antibody testing and extended RBC antigen phenotyping in patients prior to the initiation of daratumumab to aid in future transfusion requirements. A method to overcome this interference is to denature red blood cell surface CD38 by treating the RBCs with dithiotreitol (DTT), thereby preventing daratumumab from binding and affecting the IAT results.(42) It is critical that the transfusion laboratory is aware of patients receiving daratumumab and equipped with techniques to deal with interference as false-positive IATs may persist for up to 6 months.

4. Conclusion

Daratumumab is a highly effective anti-plasma cell therapy that has become integral in the treatment of multiple myeloma. It has rapidly moved from an agent used in the relapsed refractory settings to earlier in the disease course with clinical trials now exploring its efficacy in the front line setting.(43) The safety profile and tolerability of the drug make it an attractive option for patients. AL amyloidosis has distinct clinical and biological features compared to myeloma. Nevertheless elimination of the underlying plasma cell clone producing the amyloidogenic light chain has been central to the treatment of AL amyloidosis for decades. The early phase clinical trial data we have detailed above is promising and suggests daratumumab will be an important therapeutic option for AL amyloidosis in the future. MRD negativity is increasingly becoming an important endpoint in plasma cell disorders and has been shown to predict progression free and overall survival in patients with multiple myeloma.(44–47) Given the abnormal light chain is central to the pathophysiology of organ dysfunction in AL amyloidosis, complete eradication of the plasma cell clone responsible for its production and attaining deeper responses or MRD negative states are rational targets in this disorder. As described, daratumumab has shown itself to outperform other novel agents in achieving MRD negativity in multiple myeloma and yields rapid and deep responses in AL amyloidosis. This makes it an ideal agent for treatment of AL amyloidosis, and we envision it being increasingly used earlier in the disease course over the coming years. Patients with AL amyloidosis who are not eligible for ASCT have limited options, particularly those with advanced Mayo Stage who have a poor prognosis. Daratumumab has the potential to become a powerful therapeutic option in this area of unmet need for the treatment of AL amyloidosis. Clinical trials assessing subcutaneous formulations of daratumumab are currently underway with the hope of improving tolerability and reducing infusion times ([NCT03301220](#), [NCT03277105](#)). The improved tolerability of subcutaneous formulations may be particularly relevant to patients

with advanced organ involvement in AL amyloidosis, a group that usually tolerate therapy poorly. In addition a number of other monoclonal antibodies to CD38 are in development and undergoing clinical trials in multiple myeloma that are likely to also play a role in AL amyloidosis treatment in the future.(48) Despite its promise, use of daratumumab in AL amyloidosis is still in its infancy. The data need to mature to answer important questions regarding; duration of hematologic responses, organ response and long term safety and tolerability. Ultimately phase III trials are required to demonstrate its superiority to current regimens prior to establishing it as a standard of care in AL amyloidosis.

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Figure 1.

Daratumumab mechanisms of action. Upper left: daratumumab binds CD38, and its Fc fragment is bound by C1q, initiating complement cascade and resulting in a MAC which leads to cell lysis and death. Upper right: daratumumab binds CD38, and its Fc fragment is then bound by an FcR-bearing effector cell, such as a natural killer cell, leading to activation of cytotoxic processes. Bottom left: daratumumab binds CD38, and its Fc fragment is then bound by an FcR-bearing macrophage, inducing phagocytosis. Bottom right: FcR-mediated crosslinking of daratumumab induces direct cellular apoptosis. MM cell multiple myeloma cell, CDC complement-dependent cytotoxicity, MAC membrane attack complex, ADCC antibody-dependent cell-mediated cytotoxicity, ADCP antibody-dependent cellular phagocytosis. Reprinted from “Daratumumab: a first-in-class CD38 monoclonal antibody for the treatment of multiple myeloma”, by Sanchez et al, *J Hematol Oncol.* 2016;9(1):51. Copyright Sanchez et al 2016. Reprinted with permission.