Vincristine, Doxorubicin, and Dexamethasone Induction before Autologous Stem Cell Transplantation in Patients with AL Amyloidosis: A Retrospective Comparison with Frontline Stem Cell Transplantation

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Abstract:

Objective High-dose melphalan and autologous stem cell transplantation (ASCT) therapy for AL amyloidosis are now associated with reduced mortality based on the application of strict criteria. However, there is no long-term evidence concerning the performance of induction therapy with newer agents, such as bortezomib or daratumumab. Concerns regarding long-term relapse despite treatment with ASCT exist, and missing the opportunity to perform ASCT might occur if induction proves to not be efficacious and cardiac amyloidosis progression deprives the patients of a chance to receive ASCT. We herein report good amyloid control by vincristine, doxorubicin, and dexamethasone (VAD) induction therapy and argue the importance of induction therapy before ASCT.

Methods We compared patients who underwent VAD induction and ASCT (VAD+ASCT) with patients who underwent frontline ASCT in our hospital.

Patients A total of 26 patients with histologically proven AL amyloidosis were included (18 in the VAD+ASCT group and 8 in the frontline ASCT).

Results In the VAD+ASCT group, the 10-year overall survival and renal response rates were 82% and 43%, respectively. The renal response rate at two years in the VAD+ASCT group was significantly better than that in the frontline ASCT group. Although there was no significant difference in the survival rates between the two groups, the time to next treatment or death was significantly better in the VAD+ASCT group than in the the frontline ASCT group. Acute kidney injury was the most frequent reason for failure to receive two courses of VAD, and early mortality was mainly due to gastrointestinal complications.

Conclusion Considering that only those who underwent 2 courses of VAD experienced a 10-year renal response, induction therapy was deemed to be directly related to the long-term control of AL amyloidosis.

Key words: AL amyloidosis, autologous hematopoietic stem cell transplantation, VAD induction chemotherapy, nephrotic syndrome

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Introduction

AL amyloidosis is a progressive disorder caused by deposition of the light chain of an immunoglobulin derived from monoclonal plasma cells as amyloid fibrils, resulting in systemic organ dysfunction, including heart failure, nephrotic syndrome, coagulopathy, and lethal arrhythmia (1). Amyloid deposition is said to be present in the heart invariably (2), and the presence of clinically significant cardiac dysfunction or arrhythmia impacts the long-term survival (3). Achievement of a hematological response is associated with the organ response, including the renal response. However, as evidenced by a study wherein more than a 50% M protein reduction at 6 months after treatment did not indicate an improvement in the survival (4), progression can occur even with a partial response. Therefore, a partial response cannot be considered an innocuous state, as in the case of multiple myelomas (5). It is thus important to achieve a hematologic response that is as deep as possible to ensure the best prognosis.

To this end, high-dose melphalan with autologous stem cell transplantation (ASCT) is performed and has been shown to be superior to conventional chemotherapies in terms of long-term disease control (6). However, it is accompanied by a high risk of treatment-related toxicity. Since the early period of performing ASCT in the 1990s, efforts to reduce early mortality have been made, and a strict adaptation criterion was instituted, which resulted in a reduction in early mortality from 15% (7) to 5% (8). Conversely, an attempt to reduce treatment-related mortality by adjusting the dose of melphalan resulted in a tradeoff between a compromised hematological response and a reduction in mortality to 5% (9). In this manner, achieving a balance between disease eradication and treatment-related risk prevention is important, and new induction regimens with better safety profiles, such as bortezomib and daratumumab (10), are now being utilized as upfront therapy before ASCT (11). However, there are no long-term data supporting these induction therapy before ASCT; bortezomib was only recently reported to have a beneficial effect on AL amyloidosis, regardless of plasma cell burden (12); thus, the long-term advantages of this induction regimen have yet to be proven because of the relatively short follow-up period.

Vincristine, adriamycin, and dexamethasone (VAD) induction therapy, the treatment choice for multiple myeloma as an induction before ASCT to multiple myeloma (13), were used between 2004 and 2010 in our hospital to treat AL amyloidosis. We experienced a better renal response rate and lower treatment-related mortality rate in cases of ASCT with VAD induction than in cases of ASCT without any induction (mainly performed starting in 2011).

Given the above, we herein report the importance of induction therapy for AL amyloidosis long-term control.

Materials and Methods

Inclusion criteria

We extracted patient data from medical records at our hospital and included 26 patients who underwent high-dose melphalan plus ASCT for AL amyloidosis from 2004 to 2015. One patient who transferred to another hospital soon after transplantation, one with a history of receiving combination therapy of melphalan+prednisolone at a previous institution, and three with induction therapy other than VAD were excluded from the analysis. The 26 cases were divided into the VAD+ASCT group who underwent induction therapy with 2 courses of VAD (vincristine 0.4 mg, days 1-4; doxorubicin 10 mg/m², days 1-4; and dexamethasone 40 mg, days 1-4, 9-12, and 17-20) and the frontline ASCT group who underwent ASCT upfront. The criteria of eligibility for ASCT were established by our hospital, as follows: age ≤65 years old, M protein detection in serum or urine, performance status grade ≤2, no evident cardiac failure signs, left ventricular ejection fraction >45% on cardiac ultrasonography, systolic blood pressure >90 mmHg, oxygen saturation >95% on room air, serum creatinine ≤2 mg/dL, serum alkaline phosphatase ≤3 times upper normal limit, serum direct bilirubin ≤2 mg/dL, and no significant comorbid chronic diseases (including pulmonary or nervous system disease, morbid diabetes). Around the year 2010, we began to treat AL amyloidosis patients with the frontline ASCT protocol, as fluid retention after dexamethasone administration was a concern. As a result, although VAD induction was considered to be related to good stem cell collection and subsequent better peri-transplant results (14), attending physicians stopped using this regimen. In 2015, bortezomib began to be used, but these cases were excluded from this study to ensure a simple comparison of ASCT with and without the VAD induction regimen. The melphalan dose was adjusted in a case-by-case manner according to the severity of renal/cardiac disease at the clinicians’ discretion.

Ethical considerations

This post hoc retrospective cohort study aimed to clarify whether or not the use of VAD induction therapy is beneficial. This study conforms to the Declaration of Helsinki and was approved by the relevant institutional review board. Signed informed consent was obtained from all of the patients.

Endpoints

The overall survival time, time to next treatment or death (TNTD), and renal response at one and two years were evaluated. The renal response was defined as a 50% decrease (at least 0.5 g/day) in the 24-hours urinary protein level (urine protein must be >0.5 g/day pretreatment). Creatinine must not worsen by 25% over baseline. In addition, the renal response at 10 years was evaluated in the VAD+
Table 1. Patients’ Demographics of the Two Groups are Shown. For Continuous Variables, Student’s t-test was Used If the Distribution was Normal, and the Mann-Whitney U Test was Used If the Distribution was Non-normal. There was No Significant Difference between the Two Groups.

|                                | VAD+ASCT (n=18) | Frontline ASCT (n=8) | All patients (n=26) |
|--------------------------------|-----------------|---------------------|--------------------|
| Age (yr)                        | 55 [45.7, 58]   | 52 [49.7, 55.7]     | 53.5 [48.2, 58.0]  |
| Male gender                     | 11 (61%)        | 4 (50%)             | 15 (57%)           |
| Serum creatinine (mg/dL)        | 0.7 [0.6, 1.0]  | 0.9 [0.8, 1.1]      | 0.8 [0.6, 1.0]     |
| eGFR (mL/min/1.73m²)            | 82.3 [61.9, 95.4] | 56.9 [37.3, 63.4]  | 70.6 [51.8, 91.5]  |
| Alkaline phosphatase (IU/L)     | 209 [172, 262]  | 279 [211, 501]      | 218 [189, 353]     |
| Serum albumin (g/dL)            | 2.2 [1.6, 2.6]  | 1.9 [1.6, 2.5]      | 2.0 [1.6, 2.6]     |
| 24h-urinary protein (g)*        | 4.52 [2.46, 5.97] | 5.58 [2.55, 5.78] | 4.67 [2.46, 5.90]  |
| Spot urinary protein (g/gCr)    | 5.10 [2.56, 7.23] | 7.77 [6.37, 8.08]  | 6.39 [3.28, 7.97]  |
| Renal amyloid stage*            |                 |                     |                    |
| Stage I                        | 9               | 1                   | 10                 |
| Stage II                       | 8               | 6                   | 14                 |
| Stage III                      | 1               | 1                   | 2                  |
| Serum M protein                |                 |                     |                    |
| Kappa/lambda                   | 1/7             | 1/2                 | 2/9                |
| Equivocal                      | 2               | 4                   | 6                  |
| Negative                       | 8               | 1                   | 9                  |
| Urinary M protein              |                 |                     |                    |
| Kappa/lambda                   | 1/11            | 2/4                 | 3/15               |
| Equivocal                      | 2               | 1                   | 3                  |
| Negative                       | 4               | 1                   | 5                  |
| Onset symptom                  |                 |                     |                    |
| Edema                          | 8               | 6                   | 14                 |
| Dyspnea                        | 2               | 0                   | 2                  |
| GI symptom                     | 6               | 3                   | 9                  |
| Asymptomatic                   | 2               | 1                   | 3                  |
| Plasma cell percentage (%)     | 3.0 [2.0, 4.2]  | 4.4 [3.6, 5.3]      | 3.3 [2.8, 5.2]     |
| Data missing                   | 2               | 0                   | 2                  |
| Transplantation era            |                 |                     |                    |
| 2004-2009                      | 14              | 0                   | 14                 |
| 2010-2015                      | 4               | 8                   | 12                 |
| Time from diagnosis to         |                 |                     |                    |
| transplantation               | 221 [173, 269]  | 63 [56, 97]         | 194 [126, 227]     |

* One patient’s data on 24h urinary protein was missing.

VAD: vincristine, adriamycin, dexamethasone autologous stem cell transplantation, ASCT: autologous stem cell transplantation.

ASCT group. The TNTD was defined as the time to next treatment for AL amyloidosis if another therapy after ASCT was performed before the patient died; otherwise it was defined as the time to death.

**Statistical analyses**

A survival time analysis by the Kaplan-Meier curve was performed for the overall survival and TNTD. The log-rank test was applied for the statistical significance assessment. A comparison of the renal responses at 1 and 2 years using Fisher’s exact test was performed, and a p value <0.05 was considered statistically significant.

**Results**

Patient demographics by treatment groups (VAD+ASCT group and frontline ASCT group) are presented in Table 1. There were no significant differences between the two groups in the age, sex, serum creatinine, estimated glomerular filtration rate (eGFR), serum albumin, 24-hour urinary protein excretion, spot urinary protein-creatinine ratio, or plasma cell percentage; these are all known prognostic factors (15-17). The biopsy results are summarized in Table 2. All four patients who underwent an endomyocardium biopsy, all but two with kidney biopsies, and all with gastrointestinal biopsies tested positive for amyloid deposition. The results of cardiac ultrasonography (UCG), cardiac gadolinium-enhanced magnetic resonance imaging (MRI), and abdominal ultrasonography with respect to liver enlargement are summarized in Table 3. There were no statistically significant differences between the two groups with regards to UCG measurements, positivity of late gadolinium enhancement, or liver enlargement.

The Kaplan-Meier curves representing the overall survival and TNTD of the two groups are shown in Figure. Although there was no significant difference in the overall survival between the two groups, the TNTD was significantly better in the VAD+ASCT group than in the frontline ASCT group (p =0.0001). Excluding 1 case with <10 years’ follow-up, the survival rate at 10 years post-transplantation in the VAD+ASCT was 82%.

The numbers of renal response and progression cases in the two groups are indicated in Table 4. Although there was no significant difference between the two groups at one year...
post-transplantation, a significantly larger proportion of patients in the VAD+ASCT group experienced a renal response at two years than in the frontline ASCT group. The number with renal response/progression stratified by the number of VAD courses performed and melphalan dose in preconditioning are indicated in Table 5. The more courses of VAD administered, the less likely the renal progression, and the higher the dose of melphalan administered, the greater the renal response. This highlighted the importance of the melphalan dose as an important factor associated with the prognosis (18) and indicated the importance of ensuring an adequate induction therapy strength for controlling plasma cell clones. This fact was backed up by the renal response rate at 10 years, shown in Table 6. Only those with two courses of VAD administered before ASCT experienced a renal response at 10 years, and the response rate was better in those who received 200 mg/m² melphalan than in those who received 140 mg/m² melphalan.

The details of serious adverse events that led to failure of the two courses of VAD administration are shown in Table 7. A majority of those who were unable to receive two courses experienced acute kidney injury; in one case, we proceeded with the transplantation because of the possibility of cardiac amyloidosis progression, and in another case, we skipped the second VAD due to severe diarrhea. Hemodialysis was initiated in another patient after one course of VAD due to irreversible kidney dysfunction, and he received a high dose of melphalan. However, the patient ultimately died 32 months after transplantation due to an undetermined cause. Therefore, acute kidney injury is considered an important and severe complication of VAD induction therapy.

Regarding the long-term outcome of patients with only one course of VAD induction, one progressed to multiple myeloma, and another suffered from persistent nephrosis despite the disappearance of M proteinemia, resulting in the introduction of hemodialysis.

The causes of death in both the groups are presented in Table 8. In the VAD+ASCT group, there was no mortality within 100 days post-transplant. As causes of early mortality, gastrointestinal complications were frequent, with one

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**Table 2. Results of a Tissue Biopsy are Shown. N/A Indicates Patients without an Endomyocardium Biopsy.**

|                  | VAD+ASCT (n=18) | Frontline ASCT (n=8) | All patients (n=26) |
|------------------|-----------------|---------------------|---------------------|
| **Heart**        |                 |                     |                     |
| Positive         | 4               | 0                   | 4                   |
| n/a              | 14              | 8                   | 22                  |
| **Kidney**       |                 |                     |                     |
| Positive         | 16              | 8                   | 25                  |
| **GI tract**     |                 |                     |                     |
| Positive         | 18              | 8                   | 26                  |

VAD: vincristine, adriamycin, dexamethasone autologous stem cell transplantation, ASCT: autologous stem cell transplantation.

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**Table 3. Results of Cardiac Ultrasonography, Late Gadolinium Enhancement Findings in Gadolinium-enhanced Cardiac MRI, and Liver Enlargement in Abdominal Ultrasonography.**

|                        | VAD+ASCT (n=18) | Frontline ASCT (n=8) | All patients (n=26) |
|------------------------|-----------------|---------------------|---------------------|
| EF (%)                 | 70 [65, 77]     | 74 [69, 78]         | 70 [66, 78]         |
| IVST (mm)              | 10 [8, 11]      | 9 [7, 11]           | 10 [8, 11]          |
| PWT (mm)               | 9 [9, 11]       | 10 [7, 11]          | 9 [8, 11]           |
| DcT (ms)               | 186 [171, 243]  | 249 [198, 293]      | 205 [180, 263]      |

**Abdominal US**

|                    | VAD+ASCT (n=18) | Frontline ASCT (n=8) | All patients (n=26) |
|--------------------|-----------------|---------------------|---------------------|
| Liver enlargement  |                 |                     |                     |
| Positive           | 3               | 1                   | 4                   |
| Negative           | 15              | 7                   | 22                  |

**Late gadolinium enhancement**

|                  | VAD+ASCT (n=18) | Frontline ASCT (n=8) | All patients (n=26) |
|------------------|-----------------|---------------------|---------------------|
| Positive         | 7               | 2                   | 9                   |
| Negative         | 9               | 4                   | 13                  |
| Data missing     | 2               | 2                   | 4                   |

VAD: vincristine, adriamycin, dexamethasone autologous stem cell transplantation, ASCT: autologous stem cell transplantation, DcT: deceleration time, EF: ejection fraction, IVST: interventricular septum thickness, PWT: posterior wall thickness.
Figure. Kaplan-Meier curve for the overall survival of the VAD+ASCT and frontline ASCT groups (A). The frontline ASCT group had a shorter observation period than the VAD+ASCT group; thus, all patients had censored data. Numbers at risk are indicated below the graph. The p value of the log-rank test is indicated. Kaplan-Meier curve for the TNTD of the VAD+ASCT and frontline ASCT groups (B). Numbers at risk are indicated below the graph. The p value of the log-rank test is indicated. VAD: vincristine, adriamycin, dexamethasone autologous stem cell transplantation, ASCT: autologous stem cell transplantation, TNTD: time to next treatment or death.

Table 4. Renal Organ Response, EF Transition, and Hematological Resolution are Shown. A Statistically Significant Difference was Observed in the Renal Response at Two Years between the VAD+ASCT and Frontline ASCT Groups.

|                      | VAD×1/x2+ASCT | frontlin | ASCT                  |
|----------------------|---------------|---------|-----------------------|
| Renal response at 1 year | 8/18          | 2/8     |
| Renal response at 2 years | 10/18         | 1/8     *   |
| Renal progression at 1 year | 5/18          | 4/8     |
| Renal progression at 2 years | 2/18          | 5/8     *   |
| Ejection fraction recovery >10% at 1 year | 0/18          | 0/8     |
| EF deterioration >10% or death due to cardiac cause at 1 year | 2/18          | 1/8     |
| M protein disappearance at 6-12 months (serum) | 8/10          | 2/7     |
| M protein disappearance at 6-12 months (urine) | 10/14         | 3/7     |

*p=0.033 Fisher’s exact test
*p=0.020 Fisher’s exact test
*missing data/initial negative M protein/death are omitted from counting

Table 5. The Numbers of Patients with Renal Response/progression at One and Two Years are Shown According to the Number of VAD Courses Administered Pretransplant and Melphalan Dose for Conditioning.

|               | VAD×2 | VAD×1 or incomplete | None | Total |
|---------------|-------|---------------------|------|-------|
| Melphalan dose |       |                     |      |       |
| (renal response/renal progression at 2 years) |       |                     |      |       |
| 200 mg/m²     | 5 (5/0)| 2 (0/0)             | 5 (0/5)| 12 (5/5) |
| 140 mg/m²     | 7 (5/2)| 3 (0/1)             | 2 (0/0)| 12 (5/3) |
| 100 mg/m²     | 1 (0/0)| 0 (0/0)             | 0 (0/0)| 1 (0/0)  |
| 70 mg/m²      | 0 (0/0)| 0 (0/0)             | 1 (1/0)| 1 (1/0)  |
| Total         | 13 (10/2)| 5 (0/1)           | 8 (1/5)| 26 (11/8) |

colonic perforation and one hemorrhagic shock due to upper gastrointestinal bleeding. Two patients died of cardiac amyloidosis: one due to fatal arrhythmia and the other due to progression of heart failure.
Table 6. The 10-year Renal Response Rates according to the Number of VAD Courses Administered and Melphalan Dose before ASCTs.

| VADx2 | VADx1 | total |
|-------|-------|-------|
| Melphalan dose | 200 mg/m² | 80% (4/5) | 0% (0/2) | 57% (4/7) |
| renal response at 10Y/total | 140 mg/m² | 42% (3/7) | 0% (0/2) | 33% (3/9) |
| Total | 58% (7/12) | 0% (0/4) | 43% (7/16) |

Table 7. Specific Cause of Cessation of the Second Course of VADs in Patients in the VAD+ASCT Group and Their Concise Profiles.

| Case No. | Cause of cessation | Age | Sex | CA | GI | PC% | Melphalan dose | CD34 cells | Long term course |
|----------|--------------------|-----|-----|----|----|-----|---------------|------------|-----------------|
| 8        | Concern of CA (SC=3.6) | 41  | M   | E, S, D, R | 3.6 | 200 (mg/m²) | 4.31 (×10⁶/kg) | Switch to bortezomib, progression to MM |
| 10       | AKI (on dialysis) | 54  | M   | S, R | 1.8 | 140 (mg/m²) | 5.03 (×10⁶/kg) | Nephrosis despite negative M protein; hemodialysis introduction at 6 years |
| 14       | AKI | 51  | M   | S, D, I, Ce, Co, R | n/a | 140 (mg/m²) | 7.92 (×10⁶/kg) | Death at 32 months, cause unspecified |
| 17       | AKI | 48  | M   | I, Co, R | 1.9 | 200 (mg/m²) | 2.8 (×10⁶/kg) | Alive, CKD stage 4A3 |
| 20       | Severe diarrhea | 64  | F   | D | 2.8 | 140 (mg/m²) | 2.01 (×10⁶/kg) | Alive, SCr 0.48, no proteinuria. dFLC >40 |

Table 8. Causes of Death and Survival Periods are Shown for All Patients who Died after Treatment (N/A: Data Missing).

| Case No. | Induction | Age | Sex | CA | GI | PC% | Melphalan dose | CD34 cells | Cause of death | Survival time |
|----------|-----------|-----|-----|----|----|-----|---------------|------------|----------------|--------------|
| 2        | VADx2 | 63  | M   | S, D | 4.2 | 140 (mg/m²) | 2.48 (×10⁶/kg) | Pneumonia | 63 months |
| 5        | VADx2 | 62  | F   | D, R | 6.5 | 140 (mg/m²) | 1.45 (×10⁶/kg) | Septic shock | 37 months |
| 12       | VADx2 | 45  | F   | S, D | 8  | 100 (mg/m²) | 3.41 (×10⁶/kg) | VT | 123 months |
| 14       | VADx1 | 51  | M   | S, D, I, Ce, Co, R | n/a | 140 (mg/m²) | 7.92 (×10⁶/kg) | Unspecified | 31 months |
| 21       | upfront SCT | 59  | F   | S, D | 3.2 | 140 (mg/m²) | 2.68 (×10⁶/kg) | Perforation of colon | 25 days |
| 22       | upfront SCT | 50  | M   | S, D, Ce, Co | 5.2 | 200 (mg/m²) | 2.86 (×10⁶/kg) | CA progression | 67 months |
| 26       | upfront SCT | 53  | M   | S | 5.6 | 140 (mg/m²) | 1.5 (×10⁶/kg) | Upper GI bleeding | 9 days |

GI: gastrointestinal amyloid deposition, E: esophagus, S: stomach, D: duodenum, I: ileum, Ce: cecum, Co: colon, R: rectum, CA: cardiac amyloidosis, PC%: plasma cell percentage

Discussion

We herein report the 16-year outcomes of ASCT focused on the additive effect of VAD induction therapy on long-term amyloid control and treatment-related risk. Although a significant overall survival benefit was not observed in the Kaplan-Meier analyses, we observed a better TNTD and renal response at two years post-transplant in the VAD+ASCT group than in the frontline ASCT group. The effect of 2 courses of VAD induction was also highlighted in the analysis of the 10-year renal response. This fact as well as the very small number of renal responses in the frontline ASCT group concisely underscore the importance of induction therapy in treating patients with AL amyloidosis.

The drawbacks associated with induction therapy include treatment-related toxicity due to induction itself and the potential loss of the window for the transplantation durable time with sufficient cardiac functionality. Two patients with early mortality suffered from gastrointestinal complications, which are a potentially serious barrier to safe ASCT despite the fact that initial gastrointestinal symptoms are nonspecific, such as weight loss or anorexia. This, along with the fact that the endoscopy results in these two cases showed only modest upper gastrointestinal amyloid deposition, although all other cases also had gastrointestinal amyloidosis, suggests that the gastrointestinal pathology is almost universal and only a symptomatic evaluation is helpful for detecting severe complications. Therefore, clinicians should be trained in managing bleeding risk with platelet transfusion and coagulation factor replenishment. Kon et al. reported colonic hematoma formation associated with factor X decrease and hematochezia in a patient with AL amyloidosis (19). Siau et al. reported a case of duodenal perforation associated with an intestinal biopsy (20). There is an underlying frailty of the intestinal mucosa; thus, initial subtle symptoms, such as epigastric pain, as in our case, should provoke a high index of suspicion among clinicians for gas-
trointestinal perforation. Varga et al. discussed the need for induction therapy in cases with more than 10% of plasma cell clones in the bone marrow aspirate (21), despite the risk of losing the opportunity to perform transplantation (22). In the present study, almost all patients had <10% plasma cell clones. Therefore, it is important to understand that the benefits of induction therapy are restricted to those with a large plasma cell burden, and this aspect should be examined in a future study.

The 10-year renal response was 43% in the VAD+ASCT group, and the treatment response was durable. Hazenberg et al. reported the outcome of three courses of VAD induction therapy combined with ASCT (23). They concluded that induction therapy is important, but VAD should not be administered due to the risk of high treatment-related mortality. However, important background differences should be mentioned. In our series, only two patients in the VAD+ASCT group had an ejection fraction under 50%, and 15 of 18 patients had an ejection fraction over 60%; furthermore, only 9 of 18 patients had cardiac involvement. In contrast, the study of Hazenberg et al. included 4 of 12 patients who died during VAD induction therapy from cardiac causes, including cardiac toxicity, and 7 of these 12 patients had cardiac involvement. Therefore, the differences in the severity of cardiac amyloidosis might be the reason for the inferior effect of VAD induction that was observed outcomes in their study.

Another study by Perz et al. reported additional VAD therapy prior to ASCT did not increase hematological or clinical response rate (24). They found that the time from the diagnosis to treatment had the strongest impact on the prognosis. In our study, the VAD+ASCT group had a longer time to treatment, so even after taking the potential delay to treatment or transplantation into account, VAD induction therapy is still more beneficial than ASCT alone. The number of VAD cycles administered was one to five in their study, compared with two in ours; this discrepancy might have resulted in different outcomes.

The study’s limitations include the difficulty in estimating the progression of heart disease, as we did not include NT-pro BNP measurements or cardiac troponins. In addition, the lack of initial free light-chain measurement also hampered our analysis of the association between the hematologic response and the long-term survival. Furthermore, the small number of patients did not permit a statistical analysis of the removal of confounders, such as plasma cells and melphalan dose.

In conclusion, in our study, an adequate strength of VAD induction therapy contributed to the improvement in the long-term nephropathy control of AL amyloidosis. Although a recent study reported a high complete response rate with a daratumumab-containing regimen (25), the follow-up period was short (median 11.4 months), and it is too early to draw a conclusion concerning the long-term outcome. This result underscores the importance of administering induction therapy before ASCT and choosing a suitable induction regimen based on the balance between long-term amyloid control and timely transplantation. Regarding the selection of induction regimen, on a review of our cases, we concluded that VAD induction should be avoided in patients with gastrointestinal hemorrhaging sign. Considering the cardiac toxicity of the VAD regimen and the VAD induction-related mortality rates reported by other groups (23, 24), patients with severe cardiac amyloidosis and hypogammaglobulinemia need to be carefully considered for VAD regimen.

The authors state that they have no Conflict of Interest (COI).

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2859
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