

Stem cell transplant and the potential role of CAR-T cells in multiple myeloma

Nouran Sabbagh¹, Axel R. Zander^{2,3}

¹ Alfaisal University, Riyadh, KSA

² Department of Stem Cell Transplant, Huntsman Cancer Center Institute, SLC, USA

³ University of Hamburg, Germany

Professor Dr. Axel Zander, MD
Martinstr. 52, University of Hamburg, Germany

Phone: +491713135984
E-mail: axel.zander@hsc.utah.edu

Citation: Sabbagh N, Zander AR. Stem cell transplant and the potential role of CAR-T cells in multiple myeloma. *Cell Ther Transplant* 2018; 7(4): 8-15

Summary

Multiple myeloma is still an incurable cancer notwithstanding the myriads of chemo- and immunotherapies. There are more than 20,000 cases of MM diagnosed per year in the US. Bone marrow transplant is still considered the cornerstone for MM therapy, at least for now. The evident need is to revisit the conventional treatment approaches to cellular therapy, such as auto- and/or allogeneic hematopoietic stem cell transplantation (HCT), and develop the new options, like CAR-T cells. This review article will present and discuss different approaches

to modern treatment of MM, by summarizing the results of clinical studies, raising feasibility and efficiency questions, and answering some of them which have been already resolved in numerous trials performed with CAR-T cells.

Keywords

Multiple myeloma, allogeneic transplant, autologous transplant, CAR-T cells.

Multiple Myeloma and the role of transplant

Multiple myeloma is proliferation of malignant plasma cells, resulting in overproduction of monoclonal proteins. It is the second most common hematologic malignancy in the USA [1], and it had long been considered a cancer with poor prognosis. At the present time, long-term survival of 5 and 10 years is possible, due to improvement of chemotherapy protocols and development of ground-breaking immunotherapy. This trend allowed many hematologists to avoid allogeneic bone marrow transplant in a number of patients. Lenalidomide, bortezomib and newer drugs have proven their efficacy in treating MM, but a subset of patients develops resistance to this treatment.

Autologous stem cell transplantation (auto-HCT) is an integrated part of most treatment strategies. Allogeneic stem cell transplantation (allo-HCT) is still a controversial option because of increased transplant-related mortality rates (TRM). Meanwhile, some doctors prefer allogeneic grafting rather than autologous transplantation in relapse of

MM, due to long-term disease-free survival associated with allo-HCT. Some factors like chemosensitivity and karyotype influence allogeneic transplant overall survival (OS) while donor availability influence progression free survival (PFS) [2]. Its curative potential is linked to graft-versus-host disease (GVHD), a side effect of allo-HCT which may be exploited for attacking any residual tumor cells. Moreover, the T cells with chimeric antigenic receptors (CAR-T cells) are regarded as the tools for making hematologic malignancies curable within next decade. The question still exists, whether allogeneic transplant will be used as a treatment modality for MM when implementing relatively more safe immune therapy options, like CAR-T cells.

Autologous transplant, an old work-horse

Autologous hematopoietic stem cell transplantation (auto-HCT) was first introduced in the 80s as an innovative treatment, being a preferred cellular treatment available for MM therapy. It has some advantages over allogeneic BMT and is still considered a safer option. The absence of immunolog-

ical complications, like rejection and graft versus host disease (GVHD) is a major benefit, but the treatment-related toxicity cannot be overlooked. Despite multiple novel agents being developed, melphalan is still the main drug used for conditioning in the absence of other less toxic alternatives. Several alternative conditioning regimens have been studied but did not show superiority [3]. One exception may be Bendamustine, but this has not been fully explored yet [4]. Several other agents like idarubicin, etoposide, busulfan, carmustine and bortezomib were also studied as a substitute for melphalan, while none of them was shown to be superior [5], some were even more toxic than melphalan alone [6, 7], and recent studies comparing melphalan and carmustine did not show any difference in terms of TRM [8, 9]. Furthermore, there is no universal consensus, when it comes to choice of the treatment modalities. E.g., one school recommends early double autologous transplant as based on trials that found considerable difference in 7-year overall survival (OS) between single vs double autologous SCT (42 vs 21% respectively) bearing in mind the low progression-free survival (PFS) in both groups (23% vs 13% respectively) [10]. Meanwhile, other workers suggest performing it as salvage treatment to allow for longer remission. Some authors claim that this strategy can lead to shorter period of disease control and carries the risk of doubling mutations over time and, consequently, increasing drug resistance of MM cells [11]. Other workers believe that salvage therapy is still acceptable, but under certain circumstances, particularly in patients with PFS > 12 months, with first remission of less than 2 years duration [12].

Tandem ASCT had the rationale to avoid this possible clonal evolution. Total therapy 1 (TT1), the first tandem ASCT trial for newly diagnosed MM patients showed encouraging results. Consequently, TT II and III showed further improvement of the long-term PFS and OS survival [13].

Allogeneic Transplant

Allogeneic transplant is associated with sufficient TRM incidence. With introduction of reduced-intensity conditioning (RIC), the TRM rates could be reduced, but relapse has become a prominent problem [14]. Bensinger et al. in their retrospective review have reported a reduced TRM rate following RIC regimen, with HR of 0.22 (0.1-0.4) $P < 0.001$, and CR 38% vs 23% when comparing to those who received myeloablative conditioning [15]. RIC regimen showed lower TRM, but similar OS rate, due to lower PFS values. A relation was found between aGVHD and non-relapse mortality (NRM) at 2 years post transplant (24% vs 37%), and both conditions were less common in patients who received RIC treatment, despite higher incidence of chronic GVHD in RIC. Further modification of the conditioning regimen by retaining its intensity and reducing the toxicity did improve the outcome significantly [16].

The two main indications for allogeneic transplants were considered, i.e., salvage therapy after failed autologous transplant, or its usage as a part of tandem auto-allo-HCT protocols in the newly diagnosed patients [17, 18, 20]. The first approach was found to be associated with prolonged remission in multiple studies. In a prospective study conducted by Lav-

allade et al. PFS was significantly higher in allogeneic HCT group as compared to the patients who received standard therapy following failed autologous transplant [19]. A similar result was also found for the high-risk patients in a retrospective study conducted by Nair, especially with lower dose of CD3+ cells infused [21]. In CIBMTR Registry, the salvage allograft patients were compared to double autotransplant cohort between 1995-2008 with inferior results, including rate of progression, observed in the salvage allograft group. In another study, when comparing 169 relapsed patients after autotransplant, PFS was higher in allograft group but with higher NRM and similar OS rates (54% vs 53%) [22].

Some studies, however, believe that careful donor selection may improve survival in relapsed patients [21, 23], though other options are suggested by the more recent studies [24]. Donato et al. did not find statistically significant difference in cGVHD rates between related and unrelated donor group, but higher aGVHD incidence in HCTs from unrelated donors [25, 26].

Concerning allo-SCT as a part of tandem transplant, there is still no consensus on whether it is superior to the tandem ASCT or single auto-HCT. When comparing allo-auto with tandem auto-HCT, Krishnan et al. did not find better overall survival (OS) or progression-free-survival (PFS) with tandem allo-auto transplant at 3 years [27]. Among several prospective trials comparing the both treatment approaches, the three programs performed by Italian, EBMT, and DSMM working groups have revealed higher efficiency, in terms of OS and PFS for those patients who underwent allo-SCT [26].

So far, the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) has performed the largest trial which showed a weak trend for longer OS and PFS in the patients who underwent tandem ASCT, over those who had tandem auto/allo-HCT, but the results did not reach statistical significance. I.e., the respective PFS rates were 46% vs 43% ($P = 0.67$), and OS values comprised 80% vs 77%, respectively ($P = 0.19$) [28]. Bjorkstrand et al. believe that this disparity in the results can be due to differences in conditioning regimen used [29]. The results of extensive available to date are summarized in Table 1.

Disappointing results of early comparative studies seem to be more encouraging with longer follow-up. Shimoni et al. claim that most studies supporting benefits of autologous over allogeneic transplant, do not necessarily reflect accurate results, since the follow-up period is short (an average of 3 yrs), and allogeneic transplants require longer follow-up period to show the PFS plateau [35]. In his study, the PFS plateau was seen after median of 6 years of follow-up with 26% PFS and 34% OS out of 50 patients. Similar results were found by El-Cheikh et al [25] at a wider age range (28-70 y.o.), with OS and PFS of 32% & 24%, respectively. Kröger et al [23] attributes this skepticism and high-failure rates of allogeneic SCT to potential inexperience and poor selection of unrelated donors for patients. In a prospective study, 95% OR and 46% CR rates are reported following allogeneic transplant with melphalan/fludarabine-based regimen. However, PFS and OS did not differ from those reported in patients who were treated with lenalidomide and dexamethasone, and this is likely due to high NRM revealed (25% at

Table 1. Summary of results on clinical outcomes in several studies comparing auto- and allo-SCT strategies in myeloma treatment

Clinical Trial, Pts group, graft origin	Conditioning regimens	Number of cases	TRM	CR	DFS	OS levels	Reference
IFM (high risk group)	Auto: Mel200/220 mg/m ² Allo: Mel200 → Bu/Flu/ATG	219 65	5% 11%	33% 33%	0% (5y) 0% (5y)	44% (5y) 33% (5y)	[30]
Italy all cases: HLA-identical	Auto: Mel200 mg/m ² Allo: Mel200 → 2 Gy TBI	80 80	4% 10%	26% 53%	20% (4y) 42% (4y)	53% (4y) 75% (4y)	[31]
Spain all cases: HLA-identical	Auto: Bu-Mel/Mel/CBV Allo: Flu/Mel140	88 26	5% 16%	11% 33%	med: 30 m med 19 m	med: 57 m med: n.r.	[3]
HOVON all cases: HLA-identical	Auto: Mel200/FN vs Thal Auto: Mel → 2 Gy TBI	141 126	nv 14%	42% 45%	med: 30 m med 30 m	med: 60 m med: 50 m	[32]
EBMT all cases: HLA-identical	Auto: Mel200 Allo: Mel200 → 2 Gy TBI	249 91	4% 16%	41% 52%	18% (5y) 35% (5y)	58% (5y) 65% (5y)	[33]
DSMM Del13 HLA-identical +MUD transplants	Auto: Mel200 mg/m ² x 2 Allo: Mel → Mel140/Flu/ ATG	73 126	nv 16%	32% 59%	nv nv	70% (3y) 60% (3y)	[34]

1 year), despite *in vivo* T cell depletion with ATG. Therefore, a selection of unrelated donor is the key factor, and the importance of selecting a matched donor is unavoidable. With these factors combined together, a one-year NRM of less than 10% was achieved [16].

Graft-versus-myeloma effect and donor lymphocyte infusions (DLI)

The concept behind allogeneic transplant was to employ the donor's immune process to target MM cells in a process known as graft-versus-myeloma (GVM) effect but this is not inconsequential since it may be associated with GVHD. That being said, cGVHD has been considered a marker for graft-versus-myeloma effect, and many studies have shown this direct relationship. This was reflected as better OS, and PFS when studying the patients with unrelated donors from the Italian Bone Marrow Registry. Crocchiolo et al. (2009) suggest that cGVHD, along with PBSC usage, and the number of chemotherapy rounds before allo HSCT are the factors which have influence upon OS [36]. Similar results were found by Donato with 36.2% survival advantage at 5 years for the patients with cGVHD [37].

Donor leukocyte infusion was developed in an effort to avoid second transplant in relapsed MM patients following allograft transplant. According to multiple studies, DLI is related to GVM effect and could safely be used to avoid a repeated transplant in relapsed patients. Multiple studies have reported improved PFS and response rate [38-40]. In a re-

cently published study, Gröger et al. suggested using DLI as a prophylaxis to avoid relapse and improve remission. After a median follow-up of 68.7 months, they reported good 8-year PFS (43%) and OS (67%) following allogeneic transplant in 61 patients who received escalating DLI. Low GVHD incidence was also observed (33%) with no DLI related mortality [34] in the same reference. On the other hand, Edwin et al. did not observe a difference in the incidence of GVHD when the patients received DLI at less than one year *versus* > 1 year after BMT, as shown by Alyea et al. [40, 42]. In terms of DLI dose, some workers suggest lower cell doses for the patients with partial response, or persistent disease after BMT and administering higher doses to those who relapsed after BMT, since higher dosage meant higher GVHD rates, and, therefore, higher toxicity risks [39, 43]. Ayuk et al. suggests, by using low escalating doses as it is possible, to achieve remission in myeloma patients with relapsed, persistent or progressive disease post BMT [43]. Eefting et al. has found DLI effect to be limited to bone marrow infiltration and not focal progression in multiple myeloma which is defined by new onset or increase in size of plasmacytomas and lytic bone lesions [44].

It is still controversial, whether DLI should be used with novel agents as a prophylaxis to prevent post DLI relapse or not. In fact, Van de Donk et al. proposed application of novel agents, after achieving clinical response in 83.3% of his patients who did not respond to DLI at the first time and were treated with novel agents after relapse [45]. Meanwhile, Gröger et al. did not find any difference between DLI-treated group and DLI+novel agent groups [39].

State of the art: usage of CAR-T cells, autologous and allogeneic SCT in MM

The idea of recruiting the patient's own cells to fight tumor cells is not a new thing, but the obstacles are also numerous. One of these problems is to make the T cells capable of evading negative selection or central tolerance. This led to the development of affinity-enhanced cells, but it was soon found that their immune escape mechanisms may cause autoimmune disorders. Accordingly, this required a design of cytotoxic cells capable of targeting specifically tumor cells while sparing the normal cells, being a more feasible option, thus leading to design of T cells with a chimeric antigen receptor (CAR-T cells).

The idea of CAR-T cells was based on potential usage of the patient's own immunity to target malignant cells after genetic reprogramming the effector T cells, thus enabling them to detect tumor cells without affecting normal human antigens. They are considered a 'living drug', since they tend to persist for long periods of time and eventually result into significant and durable destruction of malignant cells. However, this treatment is still at its early stage of development, and has long way to go, especially, in MM, as the ideal antigen that should be targeted by CAR-T cells is still to be determined.

Broad phenotypic heterogeneity of MM is an obstacle for effective implementation of CAR-T cells. This heterogeneity originates from the various MM subclones that evolve over time within the same patient's cell population, thus making the target antigen selection even more difficult. CD138, Igk light chain, and BCMA are considered promising target antigens that were proven to be expressed by MM cells through appropriate screening studies. CD19 can be also exploited as a potential target in leukemia and lymphoma, but not in MM, due to its negligible expression in this disorder [46]. Other antigens, like CD44v6, CD70, CD56, CD38, SLAMF7, were also present on MM cell surface, but no clinical trials were done so far. Unfortunately, most of these antigens, except of BCMA and CD138, are also expressed by other populations, like normal B lymphocytes. Hence, BCMA is the ideal target that was found to be expressed exclusively by MM cells. This was concluded after comparing of MM and normal cells by flow cytometry, IHC, and ELISA techniques, and it was recently supported by 4 clinical trials studying effects of CAR-T cells in 55 patients. Four patients developed complete remission (CR), and 30 patients showed sCR or VGPR [46]. In addition, nine trials were only published as abstracts were conducted to study the efficacy of CAR-T cells in 156 patients. Of them, 31 patients showed complete response, 34 VGPR, and 28 achieved PR [47]. Further studies are essential to analyze T cell characteristic in MM and detect antigens that could predict response to CAR-T cells in MM patients, as it was the case in CLL. Some antigens were found predictive of good response to CAR-T cells in CLL patients, e.g., immune memory-related genes IL 6 and STAT3 signatures, whereas markers of glycolysis, and effector cell differentiation were found in non-responder group [48]. It is important to keep in mind the cytokine release syndrome

which is a common adverse effect of the CAR-T cell therapy. It occurs due to massive production of cytokines like IL6, TNF α , IFN γ caused by CAR-T cell activation leading to fever, hypotension, and hypoxia. Fortunately, tocilizumab (an anti IL6 antibody) may counteract the cytokine effect and is used as an off-label drug to control severe cases [49]. Therefore, it is reasonable to monitor the patient closely for at least 9 days, as the reaction appears within days to weeks of treatment initiation. Likewise, potential neurologic toxicity warrants monitoring patients for at least 14 days. The symptoms can range from headache and confusion to hallucinations, or dysphasia and coma [50].

Conclusion

Over several decades, different treatment options were developed for MM therapy, with gradually increasing success rates. At the present time, where do we stand with cellular therapies in the treatment of Multiple Myeloma?

- Tandem high-dose therapy with autologous stem cell rescue has been a component of several treatment schedules: it is a simple and inexpensive approach which is actively applied with sufficient clinical efficiency. We do not know if it is still an essential component in combination with newer drugs, but do we care? Until proven otherwise, it may stay a part of frontline of MM therapy.
- Allogeneic SCT is a challenging and widely overlooked tool. It has shown curative potential, particularly in relapsed MM. If combined with DLI and immunomodulating agents and minimal residual disease (MRD) tracing, this approach makes immunotherapy a distinct option in MM treatment. To make allogeneic SCT wider applicable and more acceptable, a reduction in TRM is mandatory, like it has been shown feasible in pilot studies.
- The results with CAR-T cells for MM treatment are very preliminary. We need longer observation terms, while looking whether CART cells could be comparable with results of allogeneic HCT. A forthcoming phase III study comparing best available treatment with CAR-T cell therapy in MM should bring a definite answer.
- It is hard to predict the future. It is conceivable, that the plethora of new drugs might override the need for cellular therapies, like we have seen in CML, i.e. control of the disease without aiming for cure.

Conflicts of interest

None of the authors declare any conflicts of interest.

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Трансплантация стволовых гемопоэтических клеток и возможная роль CAR T-клеток при лечении миеломной болезни

Нуран Саббах¹, Аксель Р. Цандер^{2,3}

¹ Университет Аль-Фейсал, Эр-Риад, Саудовская Аравия

² Отдел трансплантации стволовых клеток, Центр раковых исследований Хантсманна, Солт-Лейк-Сити, США

³ Гамбургский Университет, Гамбург, Германия

Резюме

Миеломная болезнь (МБ) остается пока неизлечимым злокачественным заболеванием, не отвечающим в полной мере на множество видов химио- и иммунотерапевтических методов лечения. В США ежегодно диагностируются более 20000 случаев. Трансплантация костного мозга все еще рассматривается как основной метод лечения МБ, по крайней мере в настоящее время. Очевидной необходимостью является повторное рассмотрение старых подходов к лечению с применением клеточной терапии, таких, как аутологичная или аллогенная трансплантация гемопоэтических стволовых клеток (ТГСК) и разработка новых опций, таких, как использование CAR-T-клеток.

Эта обзорная статья будет оценивать и обсуждать различные современные подходы к лечению МБ, путем обобщения результатов клинических исследований, рассматривать вопросы выполнимости и эффективности, и искать ответы на те из них, которые уже решены в ходе ряда клинических испытаний, проведенных с введением CAR T-клеток.

Ключевые слова

Множественная миелома, аллогенная трансплантация, аутологичная трансплантация, CAR T-клетки.