The impressive efficacy of anti-G protein-coupled receptor, class C group 5 member D chimeric antigen receptor T cells in patients with relapsed or refractory multiple myeloma

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Over the last two decades the treatment landscape for multiple myeloma (MM) has progressively expanded and includes multiple proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs) and monoclonal antibodies (MoAbs), particularly those targeting CD38 (1). Combination of these drug classes are highly effective with a tolerable safety profile and have become the new pillars of modern MM therapy for newly diagnosed as well as relapsed patients. Yet, while progression free survival (PFS) and overall survival (OS) have improved significantly with the addition of these drugs, MM still remains largely incurable prompting the search for novel and innovative treatment approaches. The resulting emergence of T cell redirecting therapy (TCRT), including chimeric antigen receptor (CAR) T cell therapy and bispecific antibodies (bsAbs) has since revolutionized the field with unprecedented response and survival rates in patients with heavily pretreated and refractory disease (2,3). B-cell maturation antigen (BCMA)-directed CAR T cell therapy was the first approved TCRT and showed impressive response rates of up to 98% in this heavily pretreated patient population (4-6). Recent updates furthermore showed long and durable remissions with BCMA-directed CAR T cell therapies with median duration of response (DOR) of 33.9 months (CARTITUDE-1) (7) and 14.8 months (KarMMa3) (8). These discoveries lead to the US food and drug administration (FDA) approval of idecabtagene vicleucel and ciltacabtagene autoleucel CAR T cell therapy in the US in early 2021 and 2022 respectively. Still, most if not all patients will eventually relapse, likely due to exhaustion of CAR T cells or loss of BCMA expression, triggering the hunt for better, more effective and durable CAR T cell constructs or alternative MM cell surface targets (9). Similar to BCMA, G protein-coupled receptor, class C, group 5, member D (GPRC5D) has uniform high expression on MM cells and has become an intense object of interest in CAR T cell therapy (10). Mailankody *et al.* were the first to report on GPRC5D targeting CAR T cell therapy in MM (11). In their study, 17 patients with relapsed/refractory disease received MCARH109, the first-in-class GPRC5D targeted CAR T cell therapy in a phase 1 dose-escalation study. The overall response rate (ORR) across all dose levels was >70%, even in patients who had prior BCMA targeting TCRT. Adverse events included cytokine release syndrome (CRS) in 88% of patients, all of them grade 1/2, except for one grade 4 event. Cytopenias, particularly lymphopenia and neutropenia was also a very common side effect and seen in all of the patients. Nail changes, rash and dysgeusia, which

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are heavily associated with GPRC5D targeting therapy were seen in 65%, 18% and 12% respectively. These unique side effects are thought to be due to GPRC5D expression in differentiating cells that produce keratin, including cortical cells of the hair follicles in the skin, the keratogenous zone of the nail and in filiform papillae of the tongue.

In the present study, Xia *et al.* conducted a single-center, single-arm, phase II trial of GPRC5D targeting CAR T cells in patients with relapsed MM at Xuzhou Medical University, China (12). Thirty-three patients were enrolled to receive the GPRC5D CAR T cell product, the vast majority had been exposed to bortezomib (100%) and lenalidomide (81%) with a quarter of them also having been exposed to anti-CD38 monoclonal antibody therapy (24%). The median lines of prior therapies was 4 (range, 2–12), 39% had a high risk cytogenetic profile, defined by the presence of deletion 17p, amplification 1q and translocations t(4;14) or t(14;16) and 39% had extramedullary disease (EMD). With a total number of 2×10^6/kg CAR T cells infused, the ORR was an impressive 91% with 75% of patients achieving at least a very good partial response (VGPR). Furthermore, 26/33 (79%) patients achieved bone marrow minimal residual disease (MRD) negativity, including 11 patients with a sCR and 9 patients with a CR. With a median follow up of 5.2 months, the data has not matured yet to comment on median DOR or median PFS, however, the authors report that at time of analysis 6/33 (18%) patients had progressed. Only 1/6 (16%) had previously achieved a CR and then progressed on D+171 of CAR T-cell infusion, while the other progressors had achieved only stable disease or less with disease progression before D+90 of CAR T-cell infusion. Of the 26 patients with MRD negativity post CAR T cell infusion, only one patient progressed. These results suggest that, similar to previous CAR T cell studies, the achievement of a CR and MRD negativity post CAR T cell infusion are heavily associated with improved clinical outcome. Furthermore, the authors include in their work some interesting sub-analysis, including response rates in patients with prior BCMA targeting CAR T cell therapy and response rates by degree of surface GRPC5D expression. Nine of 33 (27%) patients that received prior BCMA CAR T cell therapy were included in this trial and 6/9 (66%) had at least a VGPR with the remaining 3 having a PR, underscoring the efficacy of GPRC5D CAR T cells even in this heavily pretreated patient population with prior BCMA targeting CAR T cell treatment. GPRC5D expression was assessed in 29 patients and divided into patients with ≥50% expression (14/29) compared to <50% expression (15/29). Response rates in patients with ≥50% was 100% compared to 80% in patients with <50% expression. While there was no statistically significant difference between these groups, it will certainly be interesting to revisit this kind of analysis in larger patient population and more granular stratification of expression levels in the future. The authors show that there was further no significant difference in response rates by age, gender, Revised International Staging System (R-ISS) stage, cytogenetic risk and previous lines of therapy. The use of all trans retinoic acid (ATRA) as an upregulator of GPRC5D expression (13) was tested in 17/33 (52%) patients, but was not associated with better response rates. GPRC5D CAR T cell expansion peaked between days 14 and 28 post infusion with 89% and 48% of the 33 patients having detectable CAR T cells at 1 and 3 months respectively. The authors report that patients with clinical responses showed a tendency to higher peak levels than those without responses and that patients with CRS had significantly higher peak levels compared to those without CRS. The expression level of GPRC5D or the addition of ATRA had no impact on CAR T cell expansion.

Similar to the Mailankody *et al.* study the safety profile in the present trial showed mainly hematological side effects with all patients having transient grade 3/4 neutropenia and lymphopenia. Grade 3/4 anemia and thrombocytopenia were observed in approximately half the patients, 17/33 (52%) and 15/33 (45%) respectively, and were limited to the first 30 days post CAR T cell infusion. As expected, CRS was also a common adverse event and was observed in 25/33 (76%) patients, all of which were grade 1/2. Neurotoxicity in form of ICANS was seen in only 2 patients, one of them with grade 3/4. Gastrointestinal adverse symptoms, including nausea, vomiting and constipation, were seen in 13/33 (39%) patients, the vast majority of them were grade 1/2. Of interest is that skin changes appeared rather rare, the only alterations were nail changes seen in 9/33 (27%) patients with rash and dysgeusia not being reported. Of note is that one death occurred in one patient with partial response around day +30 of CAR T cell infusion, however the cause of death is not described.

Taken together, the presented study by Xia *et al.* clearly demonstrates efficacy of GPRC5D targeting CAR T cell therapy and consolidates previously seen response rates of up to 91% in pretreated MM patients. In unison with the Mailankody *et al.* study, Xia *et al.* further show that GPRC5D directed CAR T cell therapy is highly effective in patients who progressed on BCMA directed TCRT offering viable treatment options for this highly refractory patient

population. As clinicians are now gaining experience with TCRT, the sequencing of such, including bsAb and CAR T cell therapy, is a topic of high interest (14-16). Further studies to determine the optimal sequence, timing of and time interval between sequential TCRTs are underway to optimize future treatment approaches.

Additional very interesting aspects presented in these early phase studies and to be investigated in future trials with larger patient numbers are the response rate by GPRC5D expression at baseline and how GPRC5D expression changes during GPRC5D directed therapy. While both, the Xia *et al.* and Mailonkody *et al.*, studies insinuate that GPRC5D expression at baseline might not be very predictive of response, it is of interest that in 6 responders with high GPRC5D expression in the Mailonkody *et al.* study, expression levels were significantly decreased (2/6) or absent (4/6) at relapse. The loss or decrease of surface antigen, such as BCMA or GPRC5D, has recently been shown to be a mechanism of TCRT resistance caused by silencing mutations or methylation (17-19). Future TCRT applications and trials should hence determine the importance of intact antigen expression and its correlation with efficacy and DOR.

Furthermore, it will need to be determined how DOR can be improved even in patients with intact antigen preservation. While the median follow up time in the Xia *et al.* study was short (5.2 months) and did not allow for estimation of DOR, the median DOR was 7.8 months in the Mailonkody *et al.* study. This appears a bit shorter compared to the published BCMA targeting CAR T cell studies (4-6), but then again, a significant proportion of patients in the GPRC5D CAR T cell studies already had BCMA TCRT. The reason for shorter DOR with sequential TCRT is thought to be due to T cell exhaustion in the setting of continues antigen exposure and T cell stimulation with TCRT. Mechanisms to improve T cell function and reduce exhaustion are currently being investigated and include longer time interval between TCRTs to allow for better recovery (20,21). Additionally, optimizing CAR T cell expansion post infusion has also been associated with more durable responses and mechanisms to improve expansion, such as more efficient T cell constructs are underway (22).

Another aspect to consider when analyzing the present study in context with other published CAR T cell studies is that the enrolled patient population can differ significantly between institutions and more so between countries, where therapeutic practices might differ. In that sense, it is of note that in the Xia *et al.* study only 8/33 (24%) of patients were exposed to anti-CD38 moAbs and only 6/33 (18%) had a previous autologous stem cell transplant, whereas these numbers would be close to 100% in most studies in the US and other countries. The median number of therapy lines (4) as well as exposure to 2nd generation IMiDs (24%) and PIs (45%) is also lower than in previously published CAR T cell trials at other sites and in other countries (4-6,11). While the reasons for these differences are diverse, it will be important to interpret the clinical outcomes of different TCRTs in the context of the investigated patient population, as response rates and DOR tend to be better in less pre-treated patients.

Lastly, it is important to mention that there seem to be some interesting differences in the side effect profiles between the two published GPRC5D CAR T cell trials. While hematological side effects and CRS were very common across the board, the presence of skin and nail is much lower in the Xia *et al.* study and dysgeusia as an adverse event is not even reported. This is quite intriguing as GPRC5D is highly expressed on epithelial cells and in the filiform papillae of the tongue and adverse events affecting the skin, nails and taste have been widely reported in previous GPRC5D targeting MM TCRTs (11,23,24). Xia *et al.* hypothesize that patient race might be a distinguishing factor in the development of these unique cutaneous side effects. This is an interesting and valid point as epithelial thickness and hence GPRC5D expression might significantly differ between patient populations. Hence, with the expansion of targets in TCRT, the aspect of severity of side effects by race should definitely be investigated in future studies as it could guide clinicians in choosing therapeutic options for their diverse patients.

Taken together, the presents study by Xia *et al.* corroborates the efficacy of GPRC5D targeting CAR T cell therapy in relapsed/refractory MM patients. With the advent of TCRTs and our expanding knowledge how to optimize these therapies, extremely exciting times are ahead that will see improved survival and hopefully cure for our MM patients in the near future.

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