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General MM

The status of anti-BCMA CAR T-cell therapy in multiple myeloma | An interview with Dr James Kochenderfer

 **James Kochenderfer**  **Alexander Maurer**  **Emily Smith** | Feb 20, 2019

James N Kochenderfer, MD, is an investigator at the National Cancer Institute (NCI), MD, USA, working in experimental transplantation and immunology. Dr. Kochenderfer, alongside his colleagues, developed the first chimeric antigen receptor (CAR) vector targeting the B-cell maturation antigen (BCMA) in multiple myeloma (MM) and has remained at the forefront of CAR T-cell (CAR T) therapy ever since.

CAR T therapy has gained a lot of interest over recent years, bringing a brand new treatment approach to hemato–oncology. With two licensed CAR T products in lymphoma indications, and with several in phase I trials for MM, it is a rapidly evolving field bringing promising new options to the table for patients in the relapsed setting.

The MM Hub were delighted to interview Dr. Kochenderfer and understand his expert opinion of the current status of CAR T in MM. The interview, detailed below, focusses specifically on anti-BCMA CAR T therapy, potential strategies to overcome the difficulties with CAR T therapy in MM, his current focus of research and the ideal patient for CAR T therapy.

The interview was conducted by Dr. Alexander Maurer, Editor-in-Chief of the MM Hub.

AM: Alexander Maurer and JK: James Kochenderfer

AM: How do you interpret current results with anti-BCMA CAR T–cell therapy in MM?

JK: My co-workers and I published the first report of an anti-BCMA CAR in 2013.[1] We then went on to do the first clinical trial in 2014 and published the results in 2018. In our first trial we had an overall response rate (ORR) of 81%, with 63% very good partial response (VGPR) and complete response (CR), and a median event-free survival (EFS) of 31 weeks.[2] Anti-BCMA CAR trials have rapidly increased in the past couple of years with many more trials underway right now. Our results have now been confirmed in other trials with anti-BCMA CAR T cells. For example, one trial I have been involved with was using the bb2121 product and we could show a similar ORR of approximately 90%.[3,4] We find that CAR-T cells are very powerful in MM with the ability to eradicate MM cells in the bone marrow and put people in remission.

So, we see these incredible response rates and many patients do obtain significant responses that last 6 to 18 months, but many of these patients will eventually relapse. Interestingly, there are a small number of patients who maintain these very long responses. I have one patient who is still in CR after 30 months. However, it is a small fraction of patients and does not compare with the responses seen in patients with diffuse large B-cell lymphoma (DLBCL).

The fact that most patients eventually develop progressive myeloma after anti-BCMA CAR T-cell therapy is probably to do with the biology of MM. We have very active anti-BCMA CAR T products, and patients have deep responses with minimal residual disease (MRD) negative status and eradication of most of their myeloma cells. But, obviously, we are not

eradicating all myeloma cells as most patients have eventual progression of their disease. It probably has to do with the fact that MM is a more heterogeneous disease compared to B-cell lymphomas. We know that one patient can have several subclones of myeloma cells that show phenotypic and genotypic differences. This is one factor that makes the disease so difficult to treat. It is very probable that many patients relapse after anti-BCMA CAR T-cell therapy because there are subclones resistant to this therapy. In our publication, we reported one patient who had a very long remission of 56 weeks but then relapsed with large amounts of myeloma cells in the bone marrow which were BCMA negative.[2]

AM: What strategies may overcome the difficult biology of MM?

JK: We can target different antigens. BCMA is probably the best antigen we have for MM because BCMA has a very restricted expression pattern; it is only expressed on plasma cells and a very small number of B cells. Therefore, it seems to be safe compared to other antigens as it does not harm other tissues in the body.

In my opinion, the second most promising antigen is SLAMF7, also known as CD319. Its expression level seems to be very strong and consistent on MM cells. SLAMF7 has some drawbacks as it is also found on natural killer cells and on some CD8 T cells, which could cause more severe immunosuppression in a patient. At NCI we are pursuing a project to open a clinical trial using an anti-SLAMF7 CAR T cell product in the spring of this year, where we want to treat patients with MM who have failed anti-BCMA CAR T-cell therapy or whose myeloma cells are BCMA-negative. We will also treat patients who have never had CAR T-cell therapy in order to compare it to anti-BCMA CAR T-cell therapies.

In the future, the right thing to do is to target more than one antigen. It will become the standard, even for B cell malignancies, because we know that antigen expression can be lost. Initially we need to test anti-SLAMF7 CAR T alone to understand its safety before we combine it with other antigens. There is a big need to find more good antigens which we can target. We work on this in our lab, however, it is very difficult to find antigens with very restricted expression on plasma cells. Other people work on CD38 and it will be interesting to see whether CD38 can be used to successfully target MM cells without causing excessive damage to other bone marrow cells. Up to now, we have no proven MM antigen to target with CAR T cells except BCMA.

AM: What are you currently working on?

JK: We have a new clinical study at the NCI with a fully human anti-BCMA CAR (NCT03602612), which is very unique as it has only the heavy chain recognition domain; this CAR has no light chain and no linker in the antigen-recognition domain.[5] This should give it the advantage of being less immunogenic compared to other anti-BCMA CARs, which are often made of a murine light chain, heavy chain and a linker. The hope is that we can generate CAR T cells that will persist longer as they will not be rejected by the patients immune system. We have not proven it yet, as so far we have only treated six patients. This concept could also potentially facilitate the administration of multiple doses. With the current CAR T constructs it is possible that patients could develop immunity against the product which may prevent re-infusion. We hope that with the less immunogenic CAR it will make repeated treatment more effective.

Also, because our new CAR construct is smaller, it makes it easier to package into the same vector together with CARs targeting other antigens. Hopefully this will facilitate targeting multiple antigens with multiple binding domains, or multiple CARs, using the same gene therapy vector. In the future, I believe that we will be targeting at least two antigens at a time.

AM: What is the ideal patient for anti-BCMA CAR T-cell therapy?

JK: As we are in phase I right now, we treat heavily pre-treated patients. Currently, many of our patients have had more than three lines of therapy.

However, CAR T-cell therapy could move to earlier lines of treatment depending how effective it becomes. Right now, CAR T-cell therapy for first-line treatment is not appropriate; it should be used in the relapsed setting. We have a lot of therapies for MM that are much more proven, less inconvenient and safer for first-line treatment. Although we do not have the data to say with certainty in which patients anti-BCMA CAR T-cell therapy is most effective, I can see it being used more frequently in high-risk patients. We need to gather more data in these subsets of patients and I think data will accrue quickly as we have large industry sponsored trials now. In the next 1–2 years we will see which patients benefit most. We should be very optimistic with the amazing response rates which we are seeing with anti-BCMA CAR T-cell therapy in patients with 7–9 prior lines of therapy. CAR T-cell therapy is using a mechanism that is different to any other myeloma therapy we currently have. This is why I am very excited about CAR T-cell therapy and want to continue working on it. I have spent more than half of my career working on CAR T cells, and currently I work only on CAR T-cell therapy in lymphoma and MM. There are still so many new avenues we need to try to improve CAR T-cell therapy, such as targeting multiple antigens or combining CAR T cells with other therapies.

AM: Do you have any final comments?

JK: Participation of patients with advanced, relapsed MM in anti-BCMA CAR T cell trials is a reasonable thing to do because it is a treatment that is different to other treatments which they have had before. We have the open anti-BCMA CAR T cell trial at the National Institute of Health in the US (NCT03602612). Although, right now it is only for US citizens because of the complicated follow-up. I am very optimistic for the future of the work in this field.

References

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