World Journal of Clinical Sciences
ISSN: 2960-0286
DOI: 10.61784/wjcs240155

ADVANCES IN ADOPTIVE CELLULAR IMMUNOTHERAPY IN MULTIPLE MYELOMA

Rhian Bakker
Philips, Monroeville, PA, USA.

Abstract: Multiple myeloma (MM) is a malignant plasma cell tumor that is still an incurable disease. In recent years, adoptive cell therapy (ACT) has developed rapidly in hematological tumors. This article mainly reviews the application progress from bone marrow infiltrating lymphocytes to genetically modified T cells to NK cells in MM. In general, ACT therapy for multiple myeloma is gradually developing towards high specificity and strong lethality. However, finding specific target antigens and preventing toxic effects of treatment are still two major problems for ACT.
Keywords: Hematology; Multiple myeloma; Adoptive cell therapy; Bone marrow infiltrating lymphocytes; CAR-T cells; TCR-T cells; CAT-NK cells

1 BONE MARROW INFILTRATING LYMPHOCYTES

Multiple myeloma (MM) is a clonal plasma cell abnormal proliferation disease, ranking second in the incidence of hematological malignancies. It mostly occurs in the elderly and is still an incurable disease [1]. In recent years, with the application of new drugs, the survival time of multiple myeloma patients has been greatly improved, but the vast majority of patients will still relapse and/or become drug-resistant, which prompts people to find new treatments. Currently, adoptive cell therapy is attracting more and more attention from researchers.

Studies have found that patients with allogeneic transplantation show lower rates of disease relapse and higher rates of molecular remission compared with autologous stem cell transplantation, which may be caused by allogeneic lymphocyte-mediated graft disease resistance [2]. In addition, patients who relapsed after allogeneic hematopoietic stem cell transplantation showed a significant therapeutic response when T cells harvested from their original stem cell donor were infused [3]. These provide a practical basis for the feasibility of adoptive cell therapy for multiple myeloma. Simply put, adoptive cell therapy (a do p tivecelltherapy, ACT) is to expand autologous or allogeneic effector cells in vitro and then inject them back into the patient's body, and then transfer them to the lesion to identify the target cells and kill them. In recent years, adoptive cell therapy for multiple myeloma has continued to progress.

Bone marrow-infiltrating lymphocytes (marrow-infiltrating lympho-cytes, MILs) are bone marrow-derived T cells expanded in vitro using CD3/CD28 strains in the presence of tumor cells. The theoretical basis is to use endogenous T cells in the tumor microenvironment to fight tumors. Noonan et al [4] conducted a phase I clinical trial in which they evaluated the feasibility, safety and effectiveness of MILs in 25 patients with new or relapsed MM. The results showed that 6 of 22 patients who received MILs treatment after autologous stem cell transplantation achieved complete remission (CR), and 7 achieved complete remission (CR). One patient achieved partial response, and five patients had stable disease. In addition, MILs can exist in the bone marrow for a long time. The anti-tumor response of patients who obtain CR can last for one year, but the duration is still lower than expected. This may be because the number of T cells obtained is not enough, or the tumor antigens are reduced and immune Caused by escape. The application of MILs in MM is still in research progress.

2 T LYMPHOCYTES

2.1 CAR-T Cells

Chimeric antigen receptor T cells (CAR-T cells) are immune T cells extracted from patients, and then use genetic engineering technology to add an antibody that can recognize tumor cells to the T cells, and then use this "enhanced" immunity to T cells are reinfused back into the patient for treatment. Chimeric antigen receptors (CARs) are genetically modified transmembrane proteins on T cells, which contain an antigen-specific extracellular domain and an intracellular domain that mediates activation signals and have target specificity [5]. The first-generation CARs only contain the antigen recognition signal CD3ζ; the second-generation CARs contain only CD3ζ. In addition, there are costimulatory molecules such as CD28 or 4-1BB; 3rd Generation CARs have multiple intracellular signaling domains, which enhance T Cellular cytotoxicity.

When producing CAR-T cells, a major focus is to find tumor-specific antigens. Previously, patients with CD19+ refractory end-stage lymphoma and leukemia were treated with CD19-targeted A significant therapeutic response was obtained after CARTs[6]. Although CD19 It is only expressed on less than 5% of multiple myeloma cells, but Garfall et al[5] After CD19+ CARTs were used in patients with multiple myeloma who relapsed after autologous hematopoietic stem cell transplantation, a longer-lasting complete response was also observed. The researchers speculated that this was because CD19+ precursor multiple myeloma cells were killed by CARTs.

BCMA is one of the currently hotly discussed CAR-T targets in multiple myeloma, and Chinese researchers have done important work in this regard. At the 2017 American Society of Clinical Oncology (American Society of Clinical Oncology) At the Clinical Oncology (ASCO) meeting, the research group of the Hematology Department of the Second Affiliated Hospital of Xi'an Jiaotong University [7] reported on 19 cases of recurrence/ Results of infusion of BCMA-targeted CAR-T cells named LCAR-B28M for refractory multiple myeloma. The results showed that the objective response rate of the patients was 100%, of which 18 patients (95%) achieved complete remission or near complete remission (the median follow-up time was 6 months without recurrence). This treatment not only has good efficacy, but also has high safety. Most of the patients (14 cases) only developed mild or controllable cytokine release syndrome (CRS), and the remaining 5 cases did not develop CRS.

CARTs targeting kappa light chains have also been in phase I clinical trials. Among seven patients with multiple myeloma expressing kappa light chains, four patients achieved stable disease lasting 2 to 17 months without monitoring. Toxic reactions caused by T cells[8]. Other types such as targeting NY-ESO-1, CD38, CD138, CS-1 CARTs have also entered preclinical research, and preliminary studies have shown strong ability to kill multiple myeloma cells [9].

CAR-T cells have good application prospects, but one issue that cannot be ignored is their safety. The killing of a large number of tumor cells in a short period of time (tumor lysis syndrome) and the release of a large amount of cytokines (CRS) can lead to adverse reactions such as severe multi-organ failure. In addition, since the target antigen is not a specific tumor antigen, CAR-T cells will kill non-tumor normal somatic cells that express a small amount of the antigen, which also causes unpredictable toxic effects. Improving its safety is also one of the focuses of current CAR research.

In recent years, many researchers have focused on the safety issues during CAR-T cell therapy and have proposed some new designs to reduce CAR-T cell toxicity. A common strategy is to introduce suicide genes into CAR-T cells, such as inducible caspase-9 (iCas9), which encodes an apoptotic protein—— caspase 9 Gene that can be drug AP1903 Start[10]. In addition, some researchers have introduced surface antigens into CAR-T cells so that they can use monoclonal antibodies to target CART cells and eliminate them [11-12] ; There is also the introduction of inhibitory CAR (iC-AR) into CAR-T cells [13], thereby avoiding unnecessary T cell activation, etc. Most of these methods are still in the exploratory stage and require further in vitro and in vivo experimental verification.

2.2 Bispecific T Cells

Bispecific antibodies are artificial antibodies containing two specific antigen-binding sites. One end of it binds to tumor surface antigens, and the other end can stimulate T cell expansion through CD3ζ, that is, it can not only lyse target cells, but also Expand effector T cells. Compared with CAR-Ts, this type of T cells can significantly shorten the preparation time and have a simpler structure [9]. In multiple myeloma, the BCMA/CD3 bispecific antibody structure has been developed and has shown good therapeutic effects in early clinical trials. It has now entered the ramp-up stage of the dose escalation trial of Phase I clinical research. Other bispecific antibodies including CD38, CD138, CD20 and Wue-1 are also under study [14-17].

2.3 Genetically Modified T Cell Receptor

Similar to CAR-T cells, TCR-T cells are also genetically modified to improve the T cell receptor's ability to recognize and clear specific tumor antigens. But the methods used are different. CAR-T cells are genetically modified to directly target a specific antigen, while TCR-T cells are T cells that originally target tumor cells and are genetically modified to have the ability to recognize tumor antigens. Enhance. The first TCR-T cell applied to multiple myeloma was a T cell targeting NY-ESO-1. More than 60% of multiple myeloma patients were found to highly express NY-ESO-1, and its expression is consistent with multiple myeloma. It is related to the clonal evolution of myeloma and indicates a poor prognosis, which also makes it an ideal target antigen [18]. Clinical trial results showed that 20 patients who received NY-ESO-1TCR-T cells did not develop CRS, and the grade of adverse events was ≤3. In addition, this TCR-T cell existed in the body for more than 2 years, and 16 patients showed good treatment response, with a median progression-free survival (PFS) of 19.1 months. The overall survival (OS) was 32.1 months. Those patients whose disease progressed or relapsed were found to be negative for NY-ESO-1 antigen, suggesting immune escape [19]. High safety, long-term persistence, and good response to antigen-positive multiple myeloma treatment are all advantages of ESO-1/LAGE-1 TCR-T cells. However, it should also be noted that immune escape may occur, thus increasing the number of targets. It may be possible to further extend the duration of sustained remission.

3 NATURAL KILLER CELLS (NK)

In addition to T cells, NK cell-related immunotherapy is also being actively developed. NK plays an important role in innate immunity and has the ability to dissolve tumor cells and virus-infected cells. Unlike T cells, NK cells kill tumor cells and are not affected by the major histocompatibility complex (majorhistocomp atibilit y complex, MHC) restriction and does not require prior contact with the antigen. There are activating receptors and inhibitory receptors on the surface of NK cells. The activating receptors include the NCRs family, NKG2D and DNAM-1, and the inhibitory receptors include KIR (killer immunoglobulin-like receptor), CD94-NKG2, etc. Normal tissue cells express HLA Class I molecules, these molecules can bind to inhibitory molecules expressed on NK cells such as KIR to avoid killing by NK cells, while tumor cells or virus-infected cells often downregulate HLA on the cell surface. Expression of class I molecules, which triggers NK cell-mediated cell lysis [20]. However, many tumors, such as myeloma in MM, do not

lack HLA on their cell surface. Expression of class I molecules, perhaps because they avoid NK One of the mechanisms of cell killing[21].

3.1 Activated NK Cells

Before NK cells were used in multiple myeloma, they were used in patients with acute myeloid leukemia after allogeneic hematopoietic stem cell transplantation. Studies have found that after infusion of KIR ligand-incompatible NK cells, these patients showed significant therapeutic responses and prevented graft rejection and graft-versus-host disease [22]. Later, the same strategy was applied to patients with myeloma. Patients with advanced multiple myeloma received haploidentical, KIR ligand-incompatible NK cell allogeneic hematopoietic stem cell transplantation. It was found that the patient achieved durable remission and had symptoms. 50% of patients achieved near complete remission[23]. This type of NK cells is called activated NK cells, which directly knock out KIR, thereby avoiding the inhibitory signals on tumor cells and killing tumors. Currently, phase II clinical trials of NK cells for the treatment of asymptomatic multiple myeloma and relapsed high-risk multiple myeloma are also ongoing.

3.2 CARNK Cells

Similar to the principle of CAR T cells, CAR NK cells also use genetic engineering technology to add an antibody to NK cells that can recognize and kill tumor cells, thereby targeting and killing tumor cells. Currently, there are relatively few studies on CAR NK cell therapy for multiple myeloma, with China taking the lead. 1 Domestic target CD138 Research on CAR NK cells has shown that the cells have strong anti-myeloma effects in vitro and in mouse models [24], In addition, another CAR NK cell targeting CS1 also obtained the same results [25].

4 CONCLUSION AND OUTLOOK

In the past decade or so, great progress has been made in the treatment of multiple myeloma, and the progression-free survival and overall survival time of MM patients have been significantly prolonged. However, due to the two major characteristics of MM: high genome instability and high dependence on the microenvironment,, its treatment is still difficult, MM Patients often develop into relapsed/refractory disease in the end, and the disease remains an incurable malignant tumor. Adoptive cell therapy may help overcome this difficulty by having a longer lasting effect and more complete tumor killing. Results from preclinical and clinical trials of various types of adoptive cell therapies are encouraging, and these new technologies may provide a breakthrough approach to curing multiple myeloma. In general, ACT therapy for multiple myeloma is gradually developing towards high specificity and strong lethality. However, how to find specific target antigens and prevent toxic and side effects are still difficulties in adoptive cell therapy, which still requires a lot of foundation. and clinical research.

COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

REFERENCES

[1] ROLLIG C, KNOP S, BORNHAUSER M. Multiple m yeloma. Lancet, 2015, 385(9983): 2197-2208.
[2] GAHRTON G, TOUR S, HEATHER MAN P. Prognosticfactorsinallog eneicbone marrow transplant formulatip lemyeloma. Journal of Clinical On-colo gy, 1995, 13(6): 1312-1322.
[3] TRICOT G, VESOLE D H, JAGANNATH S. Graft-versus-myeloma effect: p roof of p rincip le. Blood, 1996, 87(3): 1196-1198.
[4] NOONAN K A, HUFF C A, DAVIS J. Adoptivetransferofactivated marrow-infiltrating l ym-p hocytes inducesmeasurableantitumorimmunity inthe bone marrow inmultip lemyeloma. ScienceTransla-tionalMedicine, 2015, 7(288): 288ra78.
[5] GARFALL AL, MAUS MV, HWANG WT Chimeric antigenreceptorT cells againstCD19formula-of p lemyeloma. TheNew EnglandJournal of Medicine, 2015, 373(11): 1040.
[6] GRUPP S A, KALOS M, BARRETT D. Chimericantigen receptor-modified T cells for acute l ym p hoidleukemia. The New EnglandJournalof Medicine, 2013, 368(16): 1509-1518.
[7] FAN F, ZHAO W, LIUJ. Durable remissions withBCMA-specificchimericantigen receptor (CAR)-modified T cells in p atients with refractory/relap sed multip le myeloma. JournalofClinical Oncology, 2017, 35(18 suppl): LBA3001.
[8] RAMOS C A, SAVOLDO B, B, TORRANO V Clinical responseswith T lymphocytes targeting malignancy-associatedkappa lightchains. TheJournalof ClinicalInvestigation, 2016, 126(7): 2588.
[9] RASCHE L, WEINHOLD N, MORGAN GJ. Immunologic approachesforthe treatment of multip le m yeloma. Cancer Treatment Reviews, 2017, 55: 190-199.
[10] GARGETT T, BROWN M P. Theinducible caspase-9 s uicide gene systemasa " safety switch" to limiton-tar-get, off-tumor toxicitiesofchimericantigenreceptorT cells. Frontiers inPharmacology, 2014, 5: 235.

[11] WANG X, CHANG W C, WONGC W. Atrans-gene-encodedcellsurface pol ypeptidefor selection, in vivotracking, and ablation of engineered cells. Blood, 2011, 118(5): 1255-1263.
[12] VOGLER I, NEWRZELA S, HARTMANN S. An im p roved bicistronic CD20/tCD34 vector for efficient p urificationandinvivodep letionof gene-modi-fied T cellsforadop tiveimmunotherapy. Molecular Therapy, 2010, 18(7): 1330-1338.
[13] FEDOROV VD, THEMELIM, SADELAIN M. PD-1-andCTLA-4-basedinhibitory chimericantigenreceptors (iCARs) divert off-target immunotherapy responses. Science Translational Medicine, 2013, 5 (215): 215ra172.
[14] MOOREGL, LEES H, SCHUBBERTS. Tun-ingT cellaffinity im proves efficac y andsafety ofanti-CD38 × anti-CD3bispecificantibodiesin monkeys -a potentialtherapy for multip le m yeloma. Blood, 2015, 126(23): 1798-1798.
[15] ZOU J, CHEN D, ZONG Y. Immunotherapy basedonbisp ecific T-cell engager with hIgG1 Fc sequence as a new therap eutic strategy in multip le m yeloma. CancerScience, 2015, 106(5):512-521.
[16] THAKUR A, AL-KADHIMI Z, DEOL A. In-ductionofanti-myelomacellularandhumoralimmunity b y pre-targeting clono g enicmyelomacells p rior to stem cell transplantwith T cellsarmedwithanti-CD3×anti-CD20bispecificantibody leads to transferofcellularand humoralanti-myelomaimmunity. Blood, 2013, 122 (21): 139 -139.
[17] HONEMANND, KUFERP, RIMPLER MM. A novelrecombinantbisp ecificsing lechainantibody, bsc-Wue-1×CD3, induces T-c ell-mediated cytotoxicity to-wardshuman multiple myelomacells. Leukemia, 2004, 18(3): 636-644.
[18] VAN RF, SZMANIASM, ZHANF. NY-ESO-1 is highl y expressed in poor-pro gnosis multip le m yelomaandinduces spontaneous humoraland cellular immune responses. Blood, 2005, 105(10): 3939-3944.
[19] RAPOPORT A P, STADTMAUER E A, BINDER-SCHOLl G K. NY-ESO-1-specific TCR engineered T cellsmediatesustainedantigen-specific an-titumor effects in m yeloma. Nature Medicine, 2015, 21(8): 914-921.
[20] MORETTA L, LOCATELLI F, PENDE D. KillerIg-like receptor-mediatedcontrolofnaturalkiller cellalloreactivity inhap loidenticalhematopoietic stem cell transplantation. Blood, 2011, 117(3): 764-771.
[21] FROHN C, HOPPNER M, SCHLENKE P. Anti-myelomaactivity ofnaturalkillerlym p hoc ytes. BritishJournalof Haematology, 2002, 119(3): 660-664.
[22] RUGGERIL, CAPANNIM, URBANIE. Effec-tivenessofdonornaturalkillercellalloreactivity in mismatchedhematopoietic transplants. Science, 2002, 295(5562): 2097-2100.
[23] SHI J, TRICOT G, SZMANIA S. Infusionof hap lo-identical killer immunog lobulin-like receptor ligandmismatchedNKcellsforrelap sedmyelomainthe setting of autolo gous stem cell transplantation. British Journal of Haematology, 2008, 143 (5): 641-653.
[24] JIANG H, ZHANG W, SHANGP. Transfection ofchimericanti-CD138gene enhancesnaturalkillercell activationand killing of multip le myelomacells. MolecularOncology, 2014, 8(2): 297-310.
[25] CHUJ, DENG Y, BENSON D M. CS1-specific chimericantigen receptor (CAR) -engineered natural killer cells enhance in vitro and in vivo antitumor activity against human multip le m yeloma. Leukemia, 2014, 28(4): 917-927.