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Immune-based Therapies for Hematological Malignancies: An Update by the EHA SWG on Immunotherapy of Hematological Malignancies

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Immunotherapy is revolutionizing the treatment of certain hematological malignancies and providing cure to patients even with some advanced diseases (eg, B-ALL, lymphoma). However, immunotherapy, especially cellular immunotherapy, is an emerging field and on-going research will have to address several issues to improve safety and efficacy of this novel treatment modality. There is also the need to extend the application to additional hematological malignancies. The EHA scientific working group for immunotherapy has defined major research questions for the future development of immunotherapy for patients with hematological malignancies.

The incidence of hematological malignancies continues to rise, while the underlying biological mechanisms of tumorgenesis remain unknown. The treatment landscape for hematological malignancies is diverse and immunotherapies are clearly entering the arena. Immune-based therapies for hematological malignancies aim at generating new agents, such as monoclonal antibodies, immunotoxins, engineered monoclonal antibodies called bispecific T-cell engagers, cell therapies involving cells of the innate and adoptive immune system, adoptive cell transfer therapy with T cells engineered to express chimeric antigen receptors or T-cell receptors, immune cell redirection strategies, gene modified immune cells, vaccines and checkpoint inhibitors (i.e. PD-1, CTLA-4, and IDO), which are less toxic and potentially more effective when compared to conventional chemo- and radiotherapy or even allogeneic HSCT. These various forms of immune-based therapies have shown significant promise, leading the charge in improving patient outcomes.

Monoclonal antibodies

Monoclonal antibodies are effective in a number of hematological malignancies.[1–3] Most of the current identified targets for monoclonal antibodies are also expressed on non-malignant cells.[4–6] However, in contrast with either gene-modified T cells (eg, CAR T-cells) or bispecific antibodies, the on-target toxicity of monoclonal antibodies on non-malignant cells is mostly tolerable.[7,8] New strategies to improve therapy with monoclonal antibodies include genetically engineering the structure and function of these antibodies, an approach shown to significantly improve their effectiveness.[1–3]

Vaccination strategies

Vaccines activating the autologous immune system for prevention and treatment of infections and other diseases might also have a major impact on human healthcare. Compared to other immunotherapies, such as checkpoint blockade or adoptive T cell therapy, most cancer vaccines to date have failed to demonstrate notable clinical efficacy.[9,10] One of the key obstacles to the development of an effective cancer vaccine is the difficulty in antigen selection and the requirement to overcome tolerance to self. In the past, most of the cancer vaccines were targeting tumor-associated antigens (TAAs) which are overexpressed in many cancers and were seen as universal targets for the treatment of patients with hematological malignancies. Unfortunately, TAAs are also expressed on normal tissues and, thus, central and peripheral tolerance can interfere with the efficacy of vaccination or alternatively it can induce auto-immunity/auto-reactivity against normal tissues. In contrast to these non-mutated self-

The authors have indicated they have no potential conflicts of interest to disclose.

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HemaSphere (2020) 4:4(e423). http://dx.doi.org/10.1097/HS9.0000000000000423.
Received: 14 May 2020 / Accepted: 25 May 2020

antigens, neoantigens which are derived from random somatic mutations in tumor cells and are not present in normal cells, can be recognized as non-self by the host immune system and thus be used as attractive targets for immunotherapies with potentially increased specificity, efficacy and safety.[11,12] Preclinical and clinical studies have demonstrated neoantigen-specific T cells represent the most potent tumor-reactive immune cell subpopulation. However, the inefficient presentation of neoantigens and the low clonal frequency, unfortunately, lead to a mostly very small population of neoantigen-specific cytotoxic T cells in cancer patients. Thus, vaccination with neoantigens may be required to elicit and expand the T-cell population specifically targeting neoantigens. The most frequently used adjuvants for personalized immunotherapy based on vaccines are autologous dendritic cells.[13] In some cancer patients, dendritic cell/peptide vaccines have demonstrated clinical benefit in phase III trials.

A clear shortcoming of cancer vaccines is the difficult standardization of the antigenic material and the reduced efficacy of adjuvants. Therefore, most investigators favor mixing relevant immunogenic peptides to be used directly as peptide vaccines or loaded onto dendritic cells as professional antigen-presenting cells.[13] The development of more effective adjuvants will probably also improve the efficacy of cancer vaccines, especially based on neoantigens. Alternatively, off-the-shelf dendritic cell-based vaccine strategies are developed to overcome some of these shortcomings by a fully standardized production of tumor vaccines.[14]

The post-transplant setting, especially the period following allogeneic stem cell transplantation is a potentially promising platform for vaccination due to cytoreduction and relative depletion of inhibitory accessory cells fostering greater immune responsiveness. Another source of non-self antigens especially in the setting of allogeneic stem cell transplantation are the minor histocompatibility antigens (MiHA), which are derived from single nucleotide differences between patient and donor.[15,16] MiHAs are recognized as non-self by the donor immune system and thus can be used as attractive targets for immunotherapy after allogeneic stem cell transplantation in form of vaccination.[17–20] In addition, currently clinical studies are ongoing with the HA-1 TCR in high risk hematological malignancies (Leiden, Seattle).

Donor lymphocyte infusions (DLI) and antigen-specific DLI

Donor lymphocyte infusions have been used for more than 30 years now to treat overt relapse, mixed chimerism or residual tumor cells following allogeneic stem cell transplantation.[21,22] In addition, the adoptive transfer of antigen-specific cytotoxic T lymphocytes and $CD4^+$ T-helper cells has been widely used to treat viral infections (especially CMV, EBV, adenovirus infections and more recently BK and JC viruses).[23–26] Currently early phase trials are in progress to study the role of donor lymphocyte infusions in the management of refractory, invasive fungal infections. One of the greatest challenges of the next few years will be that of transitioning the initial promising results, mainly obtained in proof-of-concept studies, to a wider application of these therapies using standardized methodological approaches.

Checkpoint inhibitors

Checkpoint inhibitor blockade releases the brakes on tumor-specific T cells, allowing them to persist and expand to attack malignant cells. Cancers can grow, at least in part, as a consequence of cancer-induced immunosuppression. In many individuals, immunosuppression is mediated by CTLA4 and PD-1, 2 immunomodulatory receptors expressed on T cells. Monoclonal antibody–based therapies targeting CTLA4 or PD-1 have shown significant clinical effects in patients with hematological malignancies, especially patients with Hodgkin's lymphoma, patients with primary mediastinal B-cell lymphoma,[27–30] and are currently being explored in several other hematological malignancies and after allogeneic transplantation despite the expected risk of increasing the rate and severity of graft versus host disease reactions.[31–33] Synergistic efficacy has been shown for CTLA4 and PD-1 blocking antibodies especially in the setting of solid tumors (eg, metastatic melanoma). Furthermore, antibodies against additional checkpoint molecules like TIM3, TIGIT, LAG-3, etc. have been developed and are being tested in early clinical trials in patients with hematological malignancies.[34,35]

Innate immune cells

Next to dendritic cells, other innate immune cells, especially natural killer (NK) cells play a key role in anti-tumor immunity.[36] NK cell function is finely tuned by both inhibitory and activating signals. NK cells do not require tumor-antigen recognition or clonal expansion before killing cancer cells. The most important inhibitory signals for NK cells are mediated via their killer immune-globulin-like receptors (KIRs), which recognize major histocompatibility complex/HLA class I antigens on autologous cells. Activating receptors bind to ligands expressed on tumor cells and induce activation of NK cells.

Recently γδ T cells, a subset of T cells expressing γδTCRs rather than the conventional αβTCR, which can exert a direct anti-tumor effect have been used for immunotherapy of hematological malignancies.[37,38] Donor-derived γδ T cells[38,39] selected after depletion of αβTCR T cells and infused following lymphodepletion were found to induce partial or even complete responses in patients with acute myeloid leukemia and multiple myeloma. In addition, infusions of NKT cells have been used in the treatment of hematological malignancies.[40,41]

Bispecific antibodies: T Cell redirecting antibodies

Bispecific antibodies that recruit and redirect T cells to attack tumor cells have tremendous potential for the treatment of hematological malignancies. These antibody constructs promote tumor cell killing by crosslinking a CD3 component of the T cell receptor complex with the tumor-associated antigen on the surface of the tumor cell. Importantly, this mode of action does not rely on a cognate interaction between the T cell receptor and a peptide/HLA complex. Thus, this strategy is not dependent on HLA restriction or on HLA expression (this representing a significant advantage since in tumors HLA class I and II molecules may be downregulated). Therefore, bispecific antibodies may find a key role in hematological malignancies with low neoantigen content and a low inflammation and these novel immunotherapeutics may productively be combined with checkpoint blockade.

Extensive optimization and process development have progressed a large number of bispecific/trispecific antibodies into clinical trials for a wide range of indications, with promising signs of therapeutic activity. As an example, Blinatumomab has already been approved for treatment of refractory, relapsed, BCP-ALL and also for patients with molecularly resistant disease

following intensive chemotherapy.[42–44] Very promising efficacy data for bispecific antibodies were demonstrated[45] in the treatment of AML and, especially, advanced multiple myeloma.

Gene-modified T cells

T cells recognize antigens through a unique antigen-specific T-cell receptor (TCR) promoting the elimination of a given target and amplifying the attack through the recruitment of other components of the immune response. T cells can target peptides derived from both intracellular and extracellular proteins, including those encoded by genes mutated in cancer cells. T cells can actively distribute within tissues and in the tumor environment, and have the potential for in vivo expansion and self-maintenance, as they can establish a memory compartment.

The last decade has witnessed technological advances, which have allowed genetic modifications of T cells providing personalized cellular therapies that target specific tumor-associated antigens. Gene transfer into human T cells can be accomplished by several means. Long-term culture of the genetically modified T cells is often required to reach meaningful clinical doses, with the functional impact of prolonged ex vivo expansion potentially adversely affecting subsequent long-term persistence in vivo. Gene delivery (or transfer) is mainly achieved through the use of viral (retroviral or lentiviral) vectors. These vectors can be manufactured to clinical grade on a large-scale producing stable integration into the genome of the T cell and its progeny. Adverse consequences due to insertional mutagenesis in T cells have not yet been reported and are unexpected given the mature differentiation status of the T cell at the time of exogenous gene integration.

However, lentiviral vectors are particularly attractive when less differentiated T cell subsets are targeted for modification, as they have the unique ability to infect T cells even upon minimal activation, a property lacking in retroviral vectors. Novel non-viral systems (eg, Sleeping Beauty and PiggyBac) allow larger fragments of DNA to be inserted than viral vectors permit.[46] These novel strategies of non-viral gene transduction are likely to reduce the cost of genetic modification of immune cells in the future by avoiding the need for large scale manufacture of clinical grade viral vectors. When combined with CRISPR/Cas (or other) gene-editing technologies, site directed insertion of the gene encoding the TCR or the chimeric antigen receptor (CAR) is achievable.[47–50] A major advantage of gene-modified T cells is that they are a living drug; thus, which can expand and proliferate in the patient. Persistence over time has been demonstrated in responding patients.

CAR T-cells

T cells redirected to specific surface antigens on malignant cells by engineered CARs are emerging as powerful therapies for hematological malignancies. In contrast to bispecific antibodies, which link the activated T cells to the tumor cells by a small molecule with binding domains for both CD3 and a surface antigen expressed on the tumor cell, here T cell are engineered to express a new antigen recognition receptor, which targets the antigen on the tumor cell surface.

An increasing number of clinical trials using CAR T-cells for the treatment of hematological malignancies have been reported, especially targeting B-cell lymphoma, BCP-ALL and multiple myeloma. Two cell products have been approved in 2017/2018 for clinical use: Kymriah (Tisagenlecleucel) and Yescarta (axicabtagene ciloleucel), which received FDA and European marketing authorization for the treatment of relapsed or refractory CD19+ BCP-ALL and for the treatment of diffuse large B-cell lymphoma (DLBCL). These approvals were based on impressive responses observed in patients with BCP-ALL including high risk patients.[51] The overall response rate and the role of complete remission in B cell lymphoma is lower than in ALL, but long-term remissions without further therapy have been reported for up to 40% of patients, enough to encourage the approval and speed up the ongoing research.[52,53] Promising initial results have been also reported in the treatment of patients with multiple myeloma, where CAR T-cells target the B-cell membrane antigen (BCMA).[54]

TCR gene-modified T cells

T cell receptor (TCR) modified T cells are a novel alternative of adoptive cell therapy designed to treat hematological malignancies and non-hematological solid tumors. Typically the genes encoding the alpha and beta chains of the TCR are cloned into retroviral or lentiviral vectors for gene transfer into autologous T cells. Novel non-viral transduction technologies, which are increasingly developed and established, are also being optimized for clinical grade TCR transfer. TCR modified T cells can mediate anti-tumor efficacy and have been used to target several antigens like NYESO-1, MAGE-A3 and PRAME, MAGE-A10 and WT1. Clinical trials have been performed to treat patients with multiple myeloma and AML.[55]

European research contributions

Europe has played a leading role in the development of bispecific antibodies. Indeed, bispecific antibodies were approved for clinical use by both the FDA and EMA after having been developed in Europe from the first pilot clinical trials until the larger phase II studies (also performed in Europe). In 2018 the FDA granted accelerated approval for the treatment of adult and pediatric patients with B-cell precursor ALL in first or second complete remission with minimal residual disease greater than or equal to 0.1%. The whole development program of Blinatumomab from the pilot trial until the final approval by the FDA and the EMA was performed under the leadership of European scientists. Currently most of the new indications for treatment of Bite/bispecific antibodies are clinically tested in Europe. New formats of bispecific antibodies are being developed by European biotech companies. Promising data on the use of bispecific antibodies also in multiple myeloma and partially in AML have been generated in European centers.[45]

Technologies of gene modification of T cells including CAR and TCR gene-transfer have been intensively developed in Europe. Patients in the UK and other EU countries have been some of the first in the world to receive these therapies outside the US. European scientists and clinicians are leading the development of gene-modified neo-antigen specific T cells, which are predicted to have a major impact in the management of sold hematological and non-hematological tumors. Other major contributions have been the development and validation of novel strategies for immune cell selection.

Despite these major contributions, Europe is currently lagging behind in the initiation of CAR T cell therapy trials, which are mainly conducted the US and China. Currently, European patients are queuing up to receive treatment with CAR T-cells for hematological malignancies in US and Chinese centers due to the

lack of open clinical trials in Europe. Of more than 400 clinical trials listed as investigating CAR T-cell therapy in the treatment of hematological or solid cancer around the world about 87% are performed in the USA and China and only a minority in Europe. The much larger pharma market, the more rapid approval for novel agents and the better support for early clinical trials explains this development.

Conclusions

Immunotherapy is revolutionizing the treatment of certain hematological malignancies and provides cure to patients even with advanced disease. Research ongoing in Europe is focusing on improving the safety and efficacy of this novel treatment modality. The goal of the future development in immunotherapy is to make it even more successful and safer as well as to extend its use to additional hematological malignancies.

Disclosures

Hermann Einsele: Consultation for BMS, Janssen, Novartis, Amgen, Takeda; Grants from BMS, Amgen, Janssen; Javier Briones: Honoraria from Roche, Takeda, Celgene, Novartis, Gilead; Consultation or advisory role for Takeda, Janssen, Celgene, Gilead/Kyte; Travel/accommodations/expenses from Roche, Takeda, Celgene, Janssen, Gilead; Fabio Ciceri: Employment/consultation for MolMed; Irene García Cadenas: Nothing to disclose; Fred Falkenburg: Financial affiliation with the Dutch Cancer Society; Natacha Bolaños: Lymphoma Coalition (LC) received grants (funds directly to LC) from Takeda, Janssen, Novartis, Amgen, Kyowa Kirin, Roche, Celgene, BMS; H.M. Mirjam Heemskerk: Grants from KWF, EU: Enacting, LUMC, Health Holland; Roch Houot: Royalties of payments for lectures/manuscript preparations from Bristol-Myers Squibb, MSD, Gilead, Kite, Roche, Novartis, Janssen, Celgene; Michael Hudecek: Royalties on patents; Franco Locatelli: Employment/consultation for Novartis, Amgen, Bellicum Pharmaceuticals, Miltenyi, Jazz, Gilead, Medac, Takeda, Jannsen; Kate Morgan: Myeloma Patients Europe (MPE) receives unrestricted, core funding from Janssen, Celgene, Novartis, Takeda, Amgen, Oncopeptides, Mundipharma, Pfizer, Roche, AstraZeneca, GSK, Sanofi; MPE receives funding from the European Commission through Horizon2020 and the Innovative Medicines Imitative; C. Emma Morris: Employment/consultation for Quell Therapeutics Limited; Grants/pending grants for NIHR, MRC, Wellcome Trust; Royalties for lectures/manuscript preparations for Gilead, Shire; Scientific founder (shares) of Quell Therapeutics Ltd; Michael O'Dwyer: Consultation with Janssen, Celgene, AbbVie, Adaptive Biotechnology; Equity in Onk Therapeutics, Carrick Therapeutics; Research support from BMS, Janssen, Onk Therapeutics; Jordi Sierra Gil: Employment/consultation for Pfizer, Amgen, Daiichi Sankyo, Astellas, Novartis, CSL Behring; Grants/pending grants from Novartis; Royalties for lectures/manuscript preparations from Astellas; Marcel van den Brink: Employment/consultation for: DKMS Chairman of the Board, WindMIL Therapeutics, Memorial Sloan Kettering Cancer Center and Sloan Kettering Institute; Grants/pending grants from R01-CA228358, R01-CA228308, R01 HL147584, MSKCC Cancer Center, NHLBI, NIA, NIAID, Tri-Institutional Stem Cell Initiative, The Lymphoma Foundation, The Susan and Peter Solomon Divisional Genomics Program, Parker Institute for Cancer Immunotherapy at Memorial Sloan Kettering Cancer Center, Seres Therapeutics (M.V.D.B); Research support from Seres Therapeutics; Consulted/received honorarium from or participated in advisory boards for Seres Therapeutics, Flagship Ventures, Novartis, Evelo, Jazz Pharmaceuticals, Therakos, Amgen, Magenta Therapeutics, WindMIL Therapeutics, Merck & Co, Inc., Acute Leukemia Forum (ALF), DKMS Medical Council (Board); Has IP Licensing with Seres Therapeutics, and Juno Therapeutics; Arjan A van de Loosdrecht: Nothing to disclose.

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