Adoptive cell therapy: challenges and promises in sarcomas

Despite some skepticism in the oncology community, cancer immunotherapy has recently and successfully made the transition from a "promising treatment" to realistic clinical applications, offering the possibility of new therapeutic opportunities even in the challenging field of advanced bone and soft tissue sarcomas (BSTS) [1].

The current immunotherapy revolution is primarily led by immune-checkpoint modulator agents that have shown impressive results against metastatic melanoma [2] and are now progressively demonstrating their efficacy in several solid tumor settings [3]. Adoptive cell immunotherapy (ACT) is benefiting from this "positive momentum" and has made limited, but important, steps into clinical applications, especially with new approaches based on lymphocytes genetically redirected against tumor targets.

BSTS have biologic features that encourage a level of optimism for successful application of immunotherapy strategies, including ACT. Sarcomas have been the historical playground for clinical immunotherapy. First observations date back to the mid 19th century, with description of sarcoma regression following wound infections and based on Coley's pioneering clinical experiments injecting inactivated bacteria broth [4]. Furthermore, over the years, crucial milestones in cancer immunology (e.g. tumor immune-surveillance, role of perforin and interferon-γ) were first demonstrated within sarcoma models [5, 6]. From a clinical perspective, however, these promising indications have not gone on to produce the expected results. Considering ACT, several approaches have been explored and there is not yet a clear indication of which strategy may be more effective against sarcomas. It is possible to schematically differentiate between approaches based on T lymphocytes directed against tumor-associated antigens (TAA) [7] and strategies exploiting immune effectors related to the innate immune system like natural killer cells (NK), γδ lymphocytes or cytokine-induced killer (CIK) cells [8].

Different biologic features of the two groups impact their potential clinical transferability and possible opportunities for synergies. Most expectations, mostly relating to the first group, relate to T lymphocytes genetically engineered with TAA-specific T cell receptors (TCR) or chimeric antigen receptors (CAR) [9]. Safety and promising clinical activity were recently reported in synovial sarcoma settings with the infusion of autologous T lymphocytes engineered with anti-NY-ESO1 TCR [10]. An important advantage of this strategy is the possible targeting of TAA derived from both extracellular and intracellular molecules, including mutation-derived neoantigens. On the other hand, however, its application is limited to

Correspondence to:
Dr. Giovanni Grignani,
Sarcoma Unit, Division of Medical Oncology
Candiolo Cancer Institute - FPO, IRCCS
Strada Provinciale 142,
10060 Candiolo (Torino), Italy.
Phone: +39 011 9933623
E-mail:giovanni.grignani@ircc.it

CANCER BREAKING NEWS 2015;3(2):3-5

patients with certain HLA-haplotypes and may be negatively affected by tumor MHC-downregulation, frequently described in sarcoma settings as an immune-escape mechanism. T-lymphocytes engineered with CARs recognize tumor targets through a single chain variable fragment derived from a TAA-specific antibody, overcoming the requirement for MHC-restriction and being potentially applicable to all patients. It is important to emphasize that CAR-engineered lymphocytes have the limitation of recognizing and targeting only extracellular tumor antigens excluding the family of cancer-testis antigens, considered very promising in sarcoma settings, and also possible neo-antigens derived by tumor-genome instability [11]. CAR-engineered lymphocytes recently showed impressive results in the field of hematologic malignancies, although these have not yet been reproduced in solid tumor settings [12-15]. Initial clinical data recently supported the safety and initial activity of T cells engineered with anti-HER2 CAR against sarcomas [16]. Objective clinical responses were not as impressive as those against hematologic tumors, but the scene is set and it is foreseeable that future trials will improve the application of this strategy to sarcoma settings. Safety is a crucial and ongoing challenge with both TCR and CAR-redirected lymphocytes. Significant and even fatal events were reported in initial trials following unexpected off-target recognitions or undesired reactions due to the low-expression of TAA in healthy organs [17]. In the sarcoma setting, cancer testis antigens are considered very promising targets given their immunogenicity and the fact that they are almost exclusively present in tumor tissues. In the next future it is conceivable that great research efforts will be directed toward identification of new mutation- and/or translocation-derived sarcoma neo-antigens, with the hope of providing suitable and effective targets for TCR-engineered lymphocytes.

As mentioned above, an intriguing alternative for ACT against sarcomas may be provided by approaches based on MHC-independent immune effectors. Interesting preclinical data have been reported with either NK or CIK cells, including data against putative sarcoma cancer stem cells [18]. Advantageous features of these strategies are the easy generation of clinically relevant rates of immune effectors with limited and cost/effective *ex vivo* manipulation. The lack of MHC-restriction indicates applicability to virtually all patients and potential avoidance of tumor immune-escape MHC-downregulation. No clinical data in the sarcoma setting are available yet but expectations are positive and clinical studies are ongoing.

The two forms of adoptive immunotherapy should not be thought of as mutually exclusive, and possible synergies may be explored in future trials. One important issue relates to when and how to integrate potentially effective ACT within the current therapeutic strategies for sarcomas. It is conceivable that, similar to other tumor settings, the ideal timing for immunotherapy is when there is minimal residual disease and this may only be found in surgically resected advanced or even metastatic sarcomas. Interesting potential options, supported by preclinical data, will be exploitation of synergies between ACT and the recently introduced immune-checkpoint modulators, or with conventional treatments like chemotherapy and/or radiotherapy.

Logistic issues affecting the clinical application of ACT for sarcomas, and tumors in general, need to be considered given the requirement for *ex vivo* manipulation, costs and need for dedicated personnel and facilities.

The solution is not simple given the requirement to comply with very rigorous and complex good manufacturing procedures (GMP) criteria. One possible scenario might include a centralization process, with generation of cell products in few specialized facilities, and constant dialogue between academic researchers and regulatory bodies. It is clear that we are experiencing an exciting time for cancer research and it is hoped that the field of sarcomas will benefit from these important advancements. The spectrum of potential approaches and synergy opportunities is constantly expanding and significant effort will be required to identify, rationalize and promote their exploration in clinical studies.

Dario Sangiolo
Laboratory of Medical Oncology-Experimental Cell Therapy – IRCCS
Department of Oncology, University of Torino, Italy

Giovanni Grignani
Medical Oncology-1, Candiolo Cancer Institute – FPO, IRCCS,
Candiolo (Torino), Italy

References

1. Mesiano G, Leuci V, Giraudo L, et al. Adoptive immunotherapy against sarcomas. Expert Opin Biol Ther 2015;15:517-28.
2. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 2015;373:23-34.
3. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab *versus* docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med 2015;373:123-35.
4. Coley WB. II. Contribution to the knowledge of sarcoma. Ann Surg 1891;14:199-220.
5. Dighe AS, Richards E, Old LJ, et al. Enhanced in vivo growth and resistance to rejection of tumor cells expressing dominant negative IFN gamma receptors. Immunity 1994;1:447-56.
6. Street SE, Cretney E, Smyth MJ. Perforin and interferon-gamma activities independently control tumor initiation, growth, and metastasis. Blood 2001;97:192-7.
7. Pollack SM, Loggers ET, Rodler ET, et al. Immune-based therapies for sarcoma. Sarcoma 2011;2011:438940.
8. Farag SS, Caligiuri MA. Human natural killer cell development and biology. Blood Rev 2006;20:123-37.
9. Davila ML, Brentjens R, Wang X, et al. How do CARs work? Early insights from recent clinical studies targeting CD19. Oncoimmunology 2012;1:1577-83.
10. Robbins PF, Morgan RA, Feldman SA, et al. Tumor regression in patients with metastatic synovial cell sarcoma and melanoma using genetically engineered lymphocytes reactive with NY-ESO-1. J Clin Oncol 2011;29:917-24.
11. Hombach AA, Heiders J, Foppe M, et al. OX40 costimulation by a chimeric antigen receptor abrogates CD28 and IL-2 induced IL-10 secretion by redirected CD4(+) T cells. Oncoimmunology 2012;1:458-66.
12. Park JR, Digiusto DL, Slovak M, et al. Adoptive transfer of chimeric antigen receptor re-directed cytolytic T lymphocyte clones in patients with neuroblastoma. Mol Ther 2007;15:825-33.
13. Mato A, Porter DL. A drive through cellular therapy for CLL in 2015: allogeneic cell transplantation and CARs. Blood 2015;126:478-85.
14. Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med 2014;371:1507-17.
15. Porter DL, Levine BL, Kalos M, et al. Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia. N Engl J Med 2011;365:725-33.
16. Ahmed N, Brawley *Vs*, Hegde M, et al. Human Epidermal Growth Factor Receptor 2 (HER2) -Specific Chimeric Antigen Receptor-Modified T Cells for the Immunotherapy of HER2-Positive Sarcoma. J Clin Oncol 2015;33:1688-96.
17. Linette GP, Stadtmauer EA, Maus MV, et al. Cardiovascular toxicity and titin cross-reactivity of affinity-enhanced T cells in myeloma and melanoma. Blood 2013;122:863-71.
18. Sangiolo D, Mesiano G, Gammaitoni L, et al. Cytokine-induced killer cells eradicate bone and soft-tissue sarcomas. Cancer Res 2014;74:119-29.