Oral Oncology 91 (2019) 123–124

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Letter to the editor

The need for combination immunotherapy in oncology

Cancer is a multifactorial disease. The term multifactorial is used to indicate that several factors including predisposing conditions and etiological factors need to occur together for a specific time duration to cause cancer. One of the most common predisposing factors for cancer is a compromised immune system. The immune system has two set of defensive lines. The first is the innate immune system, predominantly composed of natural killer (NK) cells. The NK cells are capable of recognizing the cells under stress. Stress signal can be expressed in several scenarios including uncontrolled cell division as noted in cancer cells. The inherent tropism exhibited by NK cells towards the stress signaling potentially cancerous and cancerous cells provides a non-specific yet effective natural therapeutic system [1–4]. Thus, the mere initiation of cancer is an indication that the cancer cells have overwhelmed the innate immune system.

After the initiation of cancer, the second line of defense (adaptive immune system) gets activated. The adaptive immune system consists of B and T lymphocytes. These cells are capable of recognizing the antigen in the cancer cells and respond by producing an antibody or lysing the cancer cells directly [1,4]. Recent studies have tried co-culturing antigen presenting cells (APCs) with naïve T-cells. The T-cells recognize the antigens expressed on the surface of the APCs, thus sensitizing the T-cells (effector cells) to recognize and attack similar antigens expressed by the other cells including cancer cells. Chimeric antigen receptor T cell immunotherapy is the latest modality used to propel the immune response against cancer cells carrying specific antigen targets [5]. Being antigen-specific, these customized adaptive immune responses effectively neutralize the proliferating cancer cells, curbing the progression of cancer [1,4]. Thus, the presence of widespread local invasion or metastasis is an indication that the proliferating cancer cells have overcome the resistance provided by the adaptive immune system.

Based on the above concept, two lines of immune defense (innate and adaptive) must be compromised for the initiation and progression of cancer. Given the natural ability of the immune system to inhibit cancer, researchers have focussed on re-activating parts of the immune system to fight cancer. Immunotherapy in oncology has largely focussed on adaptive immunity as it is more antigen-specific, thus could easily be manipulated to target cancer cells. The most common forms of adaptive immunotherapy include eliciting a customized immune response against a predetermined antigen (cancer cells) and introducing antibodies enabling the pre-existing T cells to attack the target (cancer) cells. Although these strategies have shown to inhibit the primary tumor, they are largely ineffective against metastatic deposits. To overcome these limitations, Sagiv Barfi et al. [4] explored the use of in-situ vaccination mediated modulation of adaptive immunity to induce a systemic immune response. Immuno-enhancing agents were locally injected at the primary tumor site, which triggered a local T cell immune response. It was found that although the trigger was local, the effect of the T-cell mediated response was noted throughout the body as elicited by the inhibition of a secondary tumor deposit at a distant site. As the study used two syngeneic tumors to represent as a primary and secondary deposit, the antigen-specific response generated against the primary tumor was capable of inhibiting the secondary tumor. In the clinical scenario, the metastatic deposit often carries additional mutations. Thus, the treatment modalities including the adaptive immunotherapy which inhibited a primary tumor may not be as effective against the metastatic deposit. In such cases, the use of a non-specific inhibitory system like the NK cell-mediated cancer cell lysis could be an effective tool to overcome the cancer resistance.

Recent studies have elicited role of tumor microenvironment in cancer progression by actively modifying the tumor cell characteristics [6] and by neutralizing the effect of the anti-cancer defense system [7]. Thus, in addition to increasing the potency of effector anti-cancer immune cells through innate and adaptive immunomodulation, it is vital to inhibit the resistance provided by the components of tumor microenvironment including cancer-associated fibroblasts, tumor activated macrophages, T regulatory cells, tumor activated neutrophils, myeloid-derived suppressor cells. The major limitation in using immune modulation is that the heightened immune response to other conventional therapeutic modalities including radio/chemotherapy and surgical interventions which may lead to increased morbidity. Thus, in such cases use of a therapeutic agent which does not elicit any adverse immune response would be optimal. One such modality is mesenchymal stem cells (MSCs). Studies have shown MSCs to possess tropism towards pathological tissues including cancer, thus providing a targeted therapy system. In addition, MSCs have immunomodulatory property thus allowing them to be introduced into a host without eliciting any significant immune response [8]. To conclude, the use of comprehensive immunotherapies (increasing the efficacy of innate and adaptive immunity in combination with inhibition of tumor microenvironment) in combination with targeted immunomodulatory anti-cancer therapeutic agents (MSCs), could aid in effectively curbing cancer without the added morbidity of conventional treatment modalities.

Conflict of interest

None declared.

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https://doi.org/10.1016/j.oraloncology.2019.02.013
Received 11 February 2019; Accepted 13 February 2019
Available online 18 February 2019
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