The RadScopal Technique to Treat Cancer

Subjects: Immunology

Contributor: Hampartsoum B. Barsoumian , Jerry Hsu , Selene Nanez , Yun Hu , Ethan Y. Hsu , Thomas S. Riad , Nahum Puebla-Osorio , Maria Angelica Cortez , James W. Welsh

The RadScopal™ technique is an innovative treatment approach that combines high-dose radiotherapy (H-XRT) directed to a primary tumor with low-dose radiotherapy (L-XRT) applied to secondary tumor(s) in patients currently undergoing or who have progressed on immunotherapy. The goal of this approach is to turn the primary tumor microenvironment (TME) into an *in-situ* vaccine that primes T-cells, while modulating the tumor stroma of secondary/metastatic lesions to enhance the infiltration and antitumor functions of effector immune cells. Furthermore, L-XRT is capable of reducing TGF-β levels and polarizing macrophages from M2 to M1 phenotype, thereby counteracting disadvantages that may be induced by H-XRT.

RadScopal Radiotherapy Immunotherapy

1. RadScopal as an Immunotherapy Booster

RadScopal immunoradiation involves both high-dose radiation in the primary tumor for immune priming and low-dose radiation in the secondary tumor for facilitating immune cell infiltration and tumor killing. Therefore, strategies that can improve either immune priming or attracting immune cells or both may enhance the treatment efficacy of RadScopal immunoradiation. NBTXR3, a hafnium oxide nanoparticle, was initially designed to increase radiation energy deposition in adjacent tumor cells [1]. It allows effective tumor destruction at a relatively low dose of radiation. In recent years, an increasing body of data has demonstrated that NBTXR3 is able to enhance antitumor immune activation in various models [2][3]. The potential of the immune modulation effect of NBTXR3 was discovered through the finding that it increases cGAS-STING pathway response [4]. Activation of the cGAS-STING pathway can lead to enhanced activation of dendritic cells, elevated expression of type I interferon, and subsequent CD8 T-cell activation [5]. The data demonstrates that NBTXR3 in combination with localized photon therapy resulted in a significant increase in tumor apoptosis in the irradiated tumors and higher CD8 T-cell infiltration in the unirradiated tumors [3]. Subsequent studies showed that the combination of NBTXR3 with RadScopal immunoradiation led to remarkable treatment efficacy in 344SQR anti-PD1 resistant metastatic lung cancer [6]. This combination therapy not only effectively contained the growth of the primary tumors that received high-dose radiation, but also eradicated secondary tumors treated with low-dose radiation. In addition, NBTXR3-mediated RadScopal immunoradiation significantly reduced the number of lung metastases. The mice treated with this combination therapy developed potent and long-term memory immune responses. Analysis of the immune landscape of the low-dose radiation-treated tumors indicates that this combination therapy reshapes T-cell repertoire, which may enhance tumor antigen recognition and targeting. Moreover, major immune pathways in tumors related to adaptive response, innate response, T-cell function, NK cell function, etc. were markedly

upregulated by NBTXR3-RadScopal radiotherapy. The researchers also observed increased infiltration of CD8 T-cells and decreased infiltration of Tregs in the low-dose radiation-treated tumors. Collectively, these findings demonstrate that NBTXR3 in combination with RadScopal radiotherapy is able to favorably modulate the tumor immune microenvironment and maximize tumor killing at the tumors that received either high-dose radiation or low-dose radiation.

Spatially fractionated radiotherapy, also known as GRID, can overcome radiation dose limitations while still preserving normal tissue function. A matrix with several pencil-like openings is used at the tumor site. Part of the tumor site is shielded by the matrix while radiation beams are delivered through the openings. From an immunological perspective, this also allows the partial sparing of immune cells in the TME that are needed for antigen presentation and priming T-cells. A clinical study of 71 patients with advanced large tumors demonstrated that single doses of 10–20 Gy had effective tumor control with no damage to epidermal and subcutaneous tissue [7]. The mass effect response was 72.5% including CR/PR, with head and neck patients benefiting the most from the utilized GRID approach. The latter can also be used at the microscopic level, which allows the delivery of greater radiation doses. Doses of up to 4000 Gy can be administered via 25 µm microbeam arrays without permanently compromising vasculature and tissue framework [8]. This could resolve lung fibrosis caused when delivering conventional therapies.

The micro-slit uses parallel beams approximately 25 µm to 75 µm wide. This provides tissue-sparing effects while allowing the administration of higher radiation doses. A preclinical murine EMT-6 carcinoma model compared cross-planar beams (410 Gy, 520 Gy, 650 Gy), vertical beams (410 Gy, 520 Gy, 650 Gy), and broad beam (30 Gy, 38 Gy, 45 Gy) treatments in murine hind legs administered as single fractions [9]. They found that toxicity and leg dysfunction were significantly lower in vertical and cross-planar beams compared to broad beams [9]. These findings suggest that micro-slit single fraction treatments have robust antitumor efficacy. Another preclinical model delivered micro-slit radiation treatment as an alternative to whole-brain radiation, as the latter has the potential for irreversible encephalon damage [10]. Doses of 96 Gy to 960 Gy for micro-slit beams and 24 Gy to 120 Gy for broad beams were used. The broad beams resulted in demyelination and hemorrhaging, whereas the micro-slit beams preserved tissue structure and function at higher doses. Currently, GRID and micro-slit radiation therapies must be further explored to determine their efficacy in the context of the RadScopal technique and their ability to spare immune cells to mount proper antitumor responses. For instance, The H-XRT portion of the RadScopal regimen can be delivered to primary tumors in form of a GRID or Lattice radiation to maintain the release of tumor-associated antigens while saving antigen-presenting cells and T-cells in surrounding tissue. On a single lesion level, GRID radiation may also be interpreted as “local RadScopal”, where high and low-dose radiation spots are created beneath the GRID matrix, resembling RadScopal on a miniature level.

2. Future Directions and Immune Oncology Drug Candidates to Combine with the RadScopal Therapy

In order to fine tune the RadScopal technique as well as predict its effect, it is critical to understand the different factors that are involved in generating the response. Considering all the factors involved allows us to explore ways

of modulating them in order to increase antitumor efficacy. The first element to consider is the selection of lesion(s) to be irradiated. Coupled with this variable is the determination of radiation dosage and fractionation which are important parameters in influencing antitumor responses [10]. In an effort to consider different radiation schemas, some mathematical models have been constructed in order to compare different radiotherapy protocols. This can allow us to determine the optimal radiation doses required to yield a robust systemic antitumor immunity [10]. Other factors that predict responses are the availability of systemic T-cells, their trafficking to tumor sites and their ability to infiltrate the TME [11]. The trafficking and infiltration of T-cells are largely aided by the L-XRT of the RadScopal technique [12]. However, other variables such as T-cell exhaustion as well as their metabolic profile within the TME can also have a serious impact on the immune response. Lastly, target lesion volume and its location play a huge role in determining treatment plans. Lesions located near critical organs may present a challenge to H-XRT, and L-XRT may be considered as an alternative to spare surrounding tissue. Given the unique biology of the RadScopal technique described above, it may provide and receive reciprocal benefits from immune agents currently under development involved in priming (signal 1), costimulation (signal 2), and activation/expansion by soluble factors (signal 3). All three signals are necessary to drive a potent T-cell activation and develop long-term memory [13].

To start with signal 1, It is previously described that H-XRT helps initiate the priming step by upregulating MHC-I and producing IFNs [14]. This step can be enhanced by combining with non-fucosylated anti-CTLA-4, a second-generation anti-CTLA-4 antibody with enhanced Treg depletion capacity, which in turn enables better priming of T-effectors (NCT04785287). A similar outcome may be achieved by using anti-CCR8 monoclonal antibody. It has been shown that tumor resident Tregs express high levels of CCR8 that can be specifically depleted by anti-CCR8 without depleting systemic Tregs [15]. This approach reduces systemic toxicity and focuses efficacy on primary as well as secondary lesions, which renders it highly suitable to combine with RadScopal. Another new approach to facilitate priming is to block CD73 expressed by stromal cells and a subset of T-cells, hence improving the availability of ATP in the TME, which serves as an energy reservoir for dendritic cells and macrophages to improve antigen presentation, a critical step in the priming process [16].

Proceeding to signal 2 and costimulation, there are several agonists tested as monotherapy or with checkpoint inhibitors, but not yet fully utilized with radiation at least on the clinical level. The importance of costimulation stems from its ability to complement the initial TCR signal and sustain the immune activation cascade, otherwise, T-cells become anergic and eventually die. Classical signal 2 agents include agonists to CD28, OX40, 4-1BB, and CD40. The RadScopal technique orchestrates both innate and adaptive immunity to systemically treat solid tumors. The innate response can be amplified by using anti-CD40 for instance, to polarize macrophages from M2 to M1 and produce a set of antitumor proinflammatory cytokines [17]. The adaptive arm on the other hand can be boosted through 4-1BB for example, to induce T-cell trafficking and generate effector and central memory [18]. Other small molecules are also under development to maintain CD28 costimulation and prolong the survival and function of T-cells and NK cells to achieve better outcomes. One such molecule is CBL-B inhibitor (CBL-Bi) that has high potential to be combined with the RadScopal approach, given the molecule's ability to liberate PI3K and AKT, and eventually activate NF-kB in T-cells and NK cells [19].

Moving forward to signal 3 to attain a complete and robust immune activation, The RadScopal technique can benefit from a wide variety of soluble factors to achieve the culmination of its potential. These include next-generation cytokine therapies, such as pegylated IL-2 (PEG-IL-2) for slow and prolonged release of IL-2, augmenting the expansion of newly primed T-cells post radiation; engineered IL-2 that binds to β and γ chains of the receptor but does not engage with the high-affinity α chain, which preferentially expands T-effectors but not Tregs [20]; engineered IL-12 cytokine that shifts the balance towards Th1 responses and polarizes macrophages to antitumor M1 phenotype [21]; and IL-15 which does not only activate and expand NK cells, but also augments T-cell memory generation on the long run [22][23].

Finally, it is critical to address activation-induced exhaustion, especially after strong combinatorial regimens with RadScopal + immune agents. To overcome this hurdle, there are checkpoint inhibitors that can be used with or without anti-PD1, to target TIM-3, LAG-3, and TIGIT on exhausted T-cells and NK cells [24], or to block intracellular downstream targets such as SHP-2 [25]. However, there are instances where the cells are terminally exhausted and hard to rejuvenate, leading to acquired resistance in conjunction with other immune evasion mechanisms deployed by tumors.

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