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Commentary

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Tumor Conditioning Regimens: An Evolution in Cancer Treatment that Relies on Short-Term Sacrifice for Long-Term Gain

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In this commentary, the authors discuss a new concept for tumor treatment, which is based on observations from published studies and clinical practice protocols. This new treatment regimen, which we coin "Tumor Conditioning Regimens," abbreviated as TCRs is based on the idea that by conditioning tumors with oxygenation, increasing mutation loads or normalizing vessels, we create a permissive environment for tumor growth in the short-term, which will eventually in the long run benefit tumor regression. In our view, such a strategy of making things worse before they get better for tumor treatment has not been articulated in the literature although anecdotal examples exist, which we have highlighted in the commentary. This commentary serves as a discussion starter for the scientific and clinical community as to the pros and cons of such an approach.

Traditional concepts in cancer treatment, including gynecologic cancers, involve using chemotherapeutic agents to target malignant cell populations, while sparing off-target effects on surrounding normal cells. This approach is based on decades of research focused on alterations within cells that allow them to become malignant and metastasize.[1] Over the last several years an increased understanding of the role of the tumor microenvironment and the host immune system in the development of cancer cell resistance to treatment has led to revisiting traditional approaches to treatment.[2] Treatment now often involves *recruiting* the host (patient) immune system and surrounding microenvironment to support and enhance the anticancer effects of treatment. With this shift in understanding of tumor biology a new concept has evolved where tumor conditioning regimens (TCR) are used that often improve conditions for tumor growth, before responses are ultimately observed. TCR is defined as, "*regimens that will influence tumor microenvironment, which may seem advantageous to tumor growth in the short run but in the long run will enable subsequent secondary treatment strategies to be more efficacious.*" The TCR concept espouses the theory that "*making things worse in the short-term will actually provide benefits in the long-term*." In this commentary, we provide three treatment examples which are current practices based on ideas of increased tumor perfusion and increased mutation burden. These practices broadly span the fields of radiation oncology, vascular biology and immune biology, and apply to gynecological cancer treatments.

The TCR concept, in our opinion, is not entirely new but clearly counterintuitive. For example, in the field of radiation oncology solid tumors, including cervical cancer, with poor oxygenation do not respond as well to radiation as tumors with adequate oxygenation.[3] Improving oxygenation to a tumor seems counterintuitive, with the concern that this could potentially allow for tumor growth. In fact, oxygen chemically modifies radiation-induced DNA damage, making it irreparable, a process known as the oxygen fixation hypothesis.[4] Therefore, methods are employed to *improve* oxygenation such as surgically decreasing tumor size prior to radiation, and administering concurrent medications that improve oxygenation during radiation.[5]

Increased oxygenation is a hallmark of angiogenesis, the growth of new blood ves-

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sels from existing vessels. The anti-vascular endothelial growth factor agent bevacizumab is used in many tumor types including ovarian and cervical cancers. In glioblastomas (GB), a malignant brain tumor known to be highly vascularized, patients treated with bevacizumab only show modest improvement in response and no improvement in overall survival.[6,7] In general, the tumor-associated vasculature is disorganized, has poor structural integrity,[8] and perfusion is poor. Vessel normalization, a concept proposed by Rakesh Jain and others, suggests that if we could convert the tumor vascular bed briefly from a pathological to a physiological angiogenesis state, subsequent therapy regimens will be effective.[9-11] This is an intriguing idea, which has concerns in that during this window of normalization, tumor cells will benefit from conditions for improved growth and metastasis. While this is possible, improved perfusion would also increase ability for treatments to penetrate tumor, and thus combining anti-angiogenics with novel therapeutics has the potential to provide a solution to this problem. We do caution the reader that additional pre-clinical research using appropriate model systems that can mimic perfusion will help gain evidence for the feasibility of this strategy.

A second example of the TCR concept involves the host immune system. Molecules on immune cells, or "checkpoints," are used to initiate or stop immune responses to foreign cells or self. T-cells express a checkpoint protein called programmed cell death protein-1 (PD-1) and when PD-1 binds to the protein programmed death ligand-1 (PD-L1) on normal cells, this signals the T-cell to not attack the normal cell.[12] Some cancer cells utilize this host defense mechanism to their advantage by carrying large amounts of PD-L1 protein that keep the immune system from attacking them.[13] Checkpoint inhibitors are used in many types of cancer and are being actively investigated for use in ovarian cancer. In melanoma, it has been shown that patients with a high mutation burden have increased neo-antigen formation and subsequent increase in response to checkpoint inhibitors.[14] Similar findings have been observed in GB patients and patients with metastatic tumors with a high frequency of somatic mutations.[15] Due to these findings, DNA *damaging* agents, such as radiation and chemotherapy, along with checkpoint inhibitors are proposed as one way to overcome resistance to immune therapy.[16] The idea of using TCR to create more DNA damage, or make the tumor "worse" (increase mutation burden for revelation of novel epitopes) to improve responses to immune therapy is a shift from traditional treatment where the goal is to target and decrease the population of cells with DNA damage.

Finally, from a clinical standpoint, as immune therapy has become more common in clinical trials, including gynecologic cancer trials, the criteria for assessing response to therapy has changed. When patients initiate immune therapy, it is common to see an initial *increase* in tumor size (pseudo-progression) before an eventual shrinkage of lesions due to activation and recruitment of the host immune system in and around the tumor. When patients are on clinical trials, a common criterion used by clinicians to determine radiological response to trial therapy is the Response Evaluation Criteria in Solid Tumors (RECIST).[17] With the initiation of immune therapy in clinical trials, a new response criteria have been developed, immune-related Response Evaluation Criteria in Solid Tumors (irRECIST)[18,19] that accounts for the initial increase in tumor size. Again, this is an example where a clinician must accommodate for an initial impression of worsening disease before an eventual improvement, which can be difficult for both the clinician and the patient.

As new treatments emerge for gynecological cancer, understanding how to make a tumor respond to therapy will need to be adjusted to incorporate not just the tumor, but the numerous surrounding host factors involved as well. Some of these modalities will involve using TCR to create initial improvement in conditions for tumor growth, which is acceptable in the short-term if the long-term outcome is regression.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest, and opinions expressed here are based on facts from scientific papers.

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