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Chapter 7

Immune Checkpoint Blockade: Subjugation of the Masses

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Additional information is available at the end of the chapter

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Abstract

Osteosarcoma remains the most common form of bone cancer in adolescents. Standard of care treatment for osteosarcoma includes chemotherapy combined with limb-salvage surgery or amputation. Survival rates for compliant patients are 60–80% for those with localized tumors and 15–30% if the tumor metastasizes or reoccurs. Given the successes of monoclonal antibody blockades in other cancers, clinical trials for applying immunotherapies to osteosarcoma are underway. Antibody blockades reinvigorate T cells to eliminate cancer cells thereby leading to decreased tumor burden and long-term regression. Single monoclonal antibody therapy has shown modest efficacy compared to standard of care. However, treating with only a single antibody can ultimately result in immune evasion by heterogeneous tumors via selection of cells expressing other inhibitory ligands. Hence, combination immunotherapies have yielded the most promising results for eliminating tumors or preventing reoccurrence in other cancer types and will likely be the most efficacious strategy for treating osteosarcoma. Here, we review current immunotherapies for other cancers and their potential application to osteosarcoma.

Keywords: osteosarcoma, monoclonal antibody blockade, PD-1, PD-L1, CTLA-4, LAG-3, TIM-3, combination antibody blockade, tumor escape

1. Introduction

Multiple tumor types have been shown to co-opt the use of immune inhibitory receptors to evade immune detection and killing [1–5], including metastatic osteosarcoma. Several immune inhibitory receptors have been identified and shown to decrease tumor-specific T-cell

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killing and induce an exhausted T-cell state [6]. The use of blocking monoclonal antibodies in experimental settings can prevent tolerance, reinvigorate T-cell function at the tumor site increasing T-cell killing, cytokine production, and proliferation, or induce new systemic T-cell responses [7]. The prevention of T-cell exhaustion or reinvigoration at the tumor site has led to improved clinical results in using these monoclonal antibodies to reduce tumor burden in human patients [8, 9]. However, outcomes after blocking monoclonal antibody therapy vary by tumor type/stage (i.e., primary versus metastatic), amount of tumor infiltrating lymphocyte (TIL) infiltration, and amount and combinational inhibitory receptor expression. Early studies investigating the role of the immune system in preventing metastatic tumor development, while allowing primary tumor growth, shed light on the importance of T-cell-tumor mingling in order to effectively suppress tumor growth through immune-mediated killing [10]. Suppressive tumor microenvironments that inhibit TIL infiltration leading to immune-privileged sites would not benefit from increased tumor-reactive T-cell responses via blocking monoclonal antibodies. Additionally, tumor-reactive T cells require inhibition via inhibitory receptors to benefit from blocking monoclonal antibody treatments [11]. Ultimately, with new advances in immunotherapies to alleviate microenvironment suppression, combinational treatments to increase T-cell function, increased immune effector access to tumors, and prevention of T-cell exhaustion may have increased curative potential.

2. Successes of single checkpoint mAb blockade strategies in the treatment of progressive tumors

2.1. PD-1 blockade

The efficacy of programmed death receptor-1 (PD-1) blockade in initial clinical trials of several tumor types has been reviewed extensively by Pardoll, Momtaz and Postow, and Sharma and Allison [9, 12, 13]. Nivolumab, pembrolizumab, and pidilizumab are α-PD-1 blocking antibodies developed by various pharmaceutical companies. Investigators are trying to identify biomarkers to classify cancer patients that will benefit most from PD-1 blockade. Programmed death ligand 1 (PD-L1) expression on tumors correlates with poor prognosis; however, high expression of PD-L1/PD-1 in tumors correlates with responses to blockade therapy [14]. However, patients with PD-L1 negative tumor expression still benefit from PD-1 blockade in some cases [15]. Briefly, overall response rate from patients with different progressive solid tumors treated with nivolumab was 31%, and duration of response was approximately 2 years, with median overall survival of 16.8 months [14, 16]. This is in comparison to malignant melanoma patients treated with pembrolizumab with an overall response rate of 38%, although treatment dose varied [17]. Additionally, chemotherapy-resistant hematologic malignancies treated with pidilizumab saw clinical benefit in 33% of patients [18]. Clinical success of the PD-1 monoclonal antibody blockade in treating multiple progressive tumors has inspired the field of tumor immunology, by leading to some of the best clinical efficacies and long-term durable regression. Currently, clinical trials for treating recurrent or refractory osteosarcoma with nivolumab, with and without ipilimumab, are in phase I/II [19].

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2.2. CTLA-4 blockade

Successes of cytotoxic lymphocyte associated antigen-4 (CTLA-4) monoclonal antibody blockade have been reviewed extensively in Ref. [13]. Briefly, patients with advanced stage melanoma when treated with ipilimumab had long-term durable responses with over 20% surviving longer than 4 years [20, 21]. However, other tumor types, such as prostate cancer, saw no improvement in survival in patients treated with ipilimumab at multiple stages of disease progression [22].

2.3. LAG-3 blockade

Lymphocyte activating gene protein 3 (LAG-3) inhibitors have begun phase I/II trials in human patients. Both renal cell carcinoma and metastatic breast cancer patients saw objective responses when treated with LAG-3 inhibitors and durable disease stabilization [23, 24]. Ongoing trials are beginning with a monoclonal antibody to LAG-3; however, no results have been reported.

2.4. TIM-3 blockade

Preclinical tumor models suggest that blocking T-cell immunoglobulin mucin domain molecule 3 (TIM-3) activation in combination with PD-1 may improve survival, as the majority of TILs are both TIM-3 and PD-1 positive, and these TILs have the most profound exhaustion at the tumor site [25]. In a mouse model of solid-tumor CT26 colon carcinoma, mice treated with dual TIM-3 and PD-1 blocking mAb had significantly decreased tumor growth; however, TIM-3 mAb treatment alone provided no benefits. The combinational approach appeared to have some synergistic effects [25].

3. Resistance to blockade treatment

3.1. Resistance to blockade treatment in tumor settings

Tumor heterogeneity provides the fuel for the evolution of therapeutic resistance [26]. A more diverse tumor has a greater likelihood of possessing a pre-existing resistance mutation than a less heterogeneous one, and a more mutable tumor has a greater likelihood of generating a *de novo* mutation during therapy. Even before immunotherapy, cells in the tumor will have undergone extensive selection for the capacity to evade the immune system during the course of progression. This means that cell-level capacities that enable resistance to immunotherapy pre-exist in some tumors. In immunotherapy, cells that preferentially survive treatment are likely to be those with the ability to create an immunosuppressive environment around the tumor and/or reduce immunogenicity through loss of antigens or downregulation of MHC I.

Taube et al. introduced the adaptive immune resistance hypothesis to explain selection of PD-L1 positive tumor cells by endogenous immune response pressure [27]. Initially proposed by Robert Schreiber, the now widely accepted hypothesis of tumor immune editing describes

how immune responses can both eliminate and promote tumor formation. This fine line between elimination and immune driven escape explains the ability of the adaptive immune resistance hypothesis to select for PD-L1 positive tumor cells, suppressing immune-mediated killing. Overwhelming evidence exists for the use of PD-1/PD-L1 blockade in reinvigorating immune-mediated tumor killing. However, little is known regarding immune-mediated tumor escape after monoclonal antibody blockade TIL reinvigoration. Responses in only a fraction of patients and incomplete tumor control from PD-1 blockade may be due to the upregulation of compensatory regulatory pathways or the selection of nonimmunogenic tumors. As stated earlier, clinical trials are in the early stages for recurring and refractory osteosarcoma treatments with monoclonal antibody blockade both as a singular drug and in combination with another monoclonal antibody blockade therapy. Therefore, little data are currently available regarding how combination immunotherapies affect human patients. Nonetheless, scientific research highly suggests increased expression of other regulatory pathways when only one immunotherapy is administered [28].

Knowing the mechanism of immune escape from blockade therapy will guide the clinician in choosing more effective treatments to combat escape and lead to durable responses or complete remission. It may also be possible to measure existing immune evasion strategies in a tumor before therapy begins in order to limit the use of immunotherapies for which the tumor may already be preadapted (e.g., where there are pre-existing resistance mutations). However, to prevent escape from occurring, it may be necessary to administer combinational treatments concurrently and early in treatment history, similar to treatment to persistent viral infections.

3.2. Viral resistance to therapy, what can we learn

T-cell exhaustion was first observed in a mouse model of chronic lymphocytic choriomeningitis virus (LCMV), in which exhausted T cells were unable to proliferate rapidly, produce antitumor cytokines, or perform cytotoxic functions [29]. PD-1 blockade in mice infected with chronic LCMV could reinvigorate T cells and rescue function. However, due to only a subset of exhausted CD8 T cells regaining function after blockade, PD-1/PD-L1 blockade is not fully effective at restoring function to all exhausted T cells [30], leaving open the potential for additional T-cell exhaustion, and ultimately viral escape. T-cell exhaustion has been observed in many chronic virally infected humans with HIV, hepatitis B virus, or hepatitis C virus, and immune checkpoint blockade can restore T-cell function *in vitro*. However, HIV escape from adaptive immune responses has led to persistent viremia with no immune control. Even in the presence of combinational antiretroviral therapy, HIV still increases inflammation, leads to increased apoptosis, and induces oxidative stress in the host. However, physicians treat with combination antiretroviral therapy at the beginning of a treatment regimen to reduce chance of viral resistance and escape.

There may be limitations to the application of viral antiresistance strategies to cancer immunotherapy including the differences in population sizes, with tumors having several orders of magnitude more cells than are typically virally infected in HIV [31, 32]. This larger population size means that there is a greater likelihood of pre-existing resistance in cancer relative to viral infections and that it may be easier for tumor cell populations to evolve resistance.

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Nonetheless, just as cancer immunologists learned from virologists about T-cell exhaustion in chronic viral settings, we may be able to apply the same strategies of early combinational treatments to try to prevent overall escape.

4. Potential escape through upregulation of other inhibitory receptors

Blockade of other inhibitory receptors in combination with PD-1 blockade is of clinical interest as responding TILs often co-express multiple inhibitory receptors, which may be an appropriate marker for potential escape through additional T-cell suppression [33].

Multiple studies have now shown increased expression of co-inhibitory receptors on infiltrating CD4 and CD8 T cells after blockade therapy including α-CTLA-4 alone, α-PD-1 alone, α-PD-L1 alone, or combinational therapies. Curran et al. observed a twofold increase in the percentage of CTLA-4+ expressing cells after treatment with anti-PD-1 mAb in their B16-BL6 melanoma mouse model [34]. Additionally, treatment with CTLA-4 mAb led to an approximate 10% increase in PD-1+ CD8+ TILs [34]. In a metastatic mouse model of osteosarcoma, treatment with anti-PD-L1 led to a twofold increase in CTLA-4 expression and selection of a PD-L1 negative tumor [28]. Sznol and Chen, in personal communications with J. Weber, confirmed this effect in human patients treated with α-PD-1 blockade noting an increase in CTLA-4 expression on TILs [35]. In an implantable mouse model of metastatic osteosarcoma, the authors of this review discovered resistance to α-PD-L1 blockade following treatment due to increases in co-inhibitory receptor expression on TILs, which dual CTLA-4/PD-1 blockade treatment could prevent [28]. These studies confirm changes in co-inhibitory receptor expression on TILs following blockade therapy and confer additional mechanisms for tumor cells to evade immune killing in response to blockade treatment. Conversely, the other co-inhibitory receptors LAG-3 and TIM-3 appear to decrease in an methylcholanthrene (MCA) induced sarcoma model following anti-PD-1 alone, anti-CTLA-4 alone, or anti-PD-1 and anti-CTLA-4 in combination [36]. The most likely explanation for increased co-inhibitory receptors following blockade is due to compensatory mechanisms preventing pathology against persistent antigen exposure.

Tumor resistance to blockade treatment generated through additional upregulation and ligation of co-inhibitory receptors may direct physicians to treat with combinational immunotherapies to target multiple inhibitory receptors. Whereas tumor resistance to blockade treatment generated through decreased immunogenicity may warrant chemotherapy or radiation in combination with blockade to increase the expression of immunogenic antigens.

5. Successes of combinational blockade strategies

5.1. Immunotherapy combinational blockades

CTLA-4 and PD-1 combinational blockade has shown promise in clinical trials against advanced melanoma with 50% of patients in the highest dose cohort achieving objective responses and a

large reduction in tumor burden [37]. The inhibitory pathways of PD-1 and CTLA-4 appear to be nonredundant with distinct mechanisms in the maintenance of peripheral tolerance, as well as biased effects on distinct subsets of T cells, making the combination of the two of particular interest.

The combination of anti-PD-L1 or anti-PD-1 and anti-CTLA-4 mAb improved tumor control, increased IL-2 production and proliferation of CD8+ TILs, and increased the ratio of intratumoral CD8+ T cells to Tregs in the B16 melanoma mouse model [34, 38]. In the GL261 glioma model, the combination of CTLA-4 and PD-L1 mAb blockade provided long-term survival and significantly reduced the proportion of Tregs in the brain [39]. Moreover, the combination potentiated the eradication of tumors in the CT26 colon carcinoma and 4T1 breast cancer model compared to the modest effects of single-agent treatment.

In a metastatic osteosarcoma model, combining PD-L1 and CTLA-4 blockade allowed for over 50% rate in mice, while neither PD-L1 nor CTLA-4 blockade alone eliminated tumor burden. Furthermore, tumor did not come back even when mice were challenged [28].

Clinical success of α-CTLA-4 and α-PD-1 monoclonal antibodies has inspired investigators to identify other potential inhibitory receptors that modulate T-cell responses in nonredundant mechanisms. Other co-inhibitory receptors of clinical interest include LAG-3 and TIM-3 [40, 41]. Blockade of both LAG-3 and PD-1 in the Sa1N fibrosarcoma model and MC38 colon adenocarcinoma model exhibited complete tumor control with effects that appear to be synergistic compared to single-agent therapy. No effect was seen against established B16 melanoma tumors again suggesting the presence of other regulatory or resistance mechanisms [40]. The blockade of both TIM3 and PD-1 in methylcholanthrene-induced fibrosarcomas suppressed growth of established tumors and even completely cleared tumors in a small fraction of mice [41]. However, the mechanism of action of anti-TIM3 blockade alone or in combination with other immunomodulatory mAbs has not been well characterized [42]. Additionally, upregulation of PD-L1 homologs B7-H3 and B7-H4 or the induction of expression of these homologs on macrophages within the tumor microenvironment presents additional opportunities for tumors to mediate effector T-cell inhibition through PD-1, when PD-L1 mAb blockade is used [43–45].

Although the mechanisms underlying resistance to PD-1/PD-L1 blockade have not yet been clearly elucidated, the success of combinational immunotherapies suggests that tumors use multiple and nonoverlapping mechanisms of resistance in order to maintain an immunosuppressive environment or to escape T-cell recognition altogether. Combinational treatment with monoclonal inhibitory blockade antibodies may be necessary for optimal anti-tumor responses and prevention of additional escape mechanisms through other T-cell inhibitory receptor suppression. Therefore, the type of blockade-driven tumor resistance may alter the choice of combinational therapies.

6. Decreased immunogenicity leading to escape

Another possible mechanism of acquired resistance to PD-1/PD-L1 blockade includes the selection of nonimmunogenic tumors [46]. Loss of antigens or downregulation of MHC I allow the

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tumor to escape from T-cell recognition, possibly following blockade reinvigoration. There is currently no evidence that we are aware of for selection of tumors with decreased immunogenicity after monoclonal antibody blockade therapy, although selection of PD-L1+ tumors during initial tumor immune responses suggests that similar mechanisms may exist following TIL reinvigoration with checkpoint inhibitor blockade. The use of radiation to overcome this type of resistance has shown promise by causing immunogenic cell death. After radiation, tumors upregulate MHC I, Fas (CD95), ICAM-1, and NKG2D ligands to become optimized targets for CTLs and lead to the release of more tumor antigens and activation of a broader T-cell repertoire [47]. Significant tumor regression in metastatic melanoma patients was seen with combinational anti-CTLA-4 blockade and radiation [48]. Another study showed the combination of radiation and PD-L1 blockade was more effective than either single agent treatment in TUBO breast cancer and MC38 colon adenocarcinoma tumor models, reduced myeloid derived suppressor cells (MDSCs), and led to eradication of tumor and protection against further rechallenge [49]. Hypofractionated radiotherapy appears to be more effective than single high-dose radiotherapy, and the combination of hypofractionated radiation with anti-PD-1 mAb increased tumor antigen–specific CD8 T cells, improved survival, increased tumor control, and elicited the abscopal effect in 4T1 and B16 tumor models [50]. Additionally, fractioned radiation required concurrent administration of PD-1 or PD-L1 to elicit a synergistic effect in CD26 colon carcinoma, 4434 melanoma, and 4T1 breast cancer models, and no synergistic effect was seen if blockade was administered sequentially after completion of radiation [51]. Combination of PD-1 blockade with targeted therapies such as BRAF inhibitors in melanoma—which has been shown to decrease IL-10 production and enhance expression of tumor-specific antigens—may also prove promising, and clinical trials of the combination are underway [52–54]. Chemotherapy can also cause immunogenic cell death and lead to maturation and recruitment of antigen presenting cells (APCs), upregulation of antigens, increased MHC I expression, and increased CD8+ TIL infiltration [55]. α-PD-1/PD-L1 mAb treatment can select for nonimmunogenic tumors via antigen loss, MHC downregulation, selection of less immunogenic antigens, etc. Combinational therapies that increase TIL repertoire, antigen diversity, and tumor-specific antigens can combat this type of resistance after PD-1/PD-L1 blockade.

Another opportunity in designing combinatorial treatments from an evolutionarily informed perspective is that of shaping selection pressures so as to make resistant cells least fit by using antagonistic drug interactions [56]. This approach uses two therapeutic agents with antagonistic effects, making the fitness of cells with resistance to one therapy or the other less fit than cells that lack resistance entirely. This strategy could potentially be leveraged in immunotherapy by employing immunotherapeutic approaches that have some antagonistic effects.

7. Conclusion

Therapeutic resistance is one of the most difficult challenges in cancer treatment. At its root, this therapeutic resistance is driven by heterogeneity of cancer cells and their capacity to evolve quickly in response to treatments. From an evolutionary perspective, immunotherapy offers a unique approach that can harness the power of the adaptive immune systems to generate and

respond to novelty rapidly and with a precision that may not be possible with other treatment approaches.

There are several potential mechanisms of resistance to PD-1/PD-L1 blockade that lead to upregulation of co-expression of inhibitory receptors and/or selection of less immunogenic tumors. Understanding these mechanisms will provide the opportunity to develop the right combination of therapies or to develop new therapies in order to elicit a potent anti-tumor T-cell response.

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