systemic anti-PD1 was able to significantly improve abscopal effect in 344SQR murine metastatic lung cancer model, most of the mice eventually died due to the growth of secondary tumors. Therefore, we intended to use HD-XRT plus NBTXR3 injection into primary tumors and low-dose (LD) radiation on secondary tumors plus dual-agent immunotherapy (IT) of anti-PD1 and anti-CTLA-4 to achieve complete control of both the primary and secondary tumors in mice.

Methods

Five groups of 8 mice each were inoculated subcutaneously with 5 × 104 anti-PD1-resistant 344SQR cells in each hind leg, 3 days apart, to establish ‘primary’ (right) and ‘secondary’ (left) tumors. All mice in treatment groups received intraperitoneal anti-PD1 and anti-CTLA-4 on days 4, 7, 10, and 13, and continuing anti-PD1 treatment on days 20, 27, 34, 41, and 49 and 12Gy x3 (HD-XRT) to the primary tumors on days 7, 8 and 9. Primary tumors in groups 3 and 5 also received intratumoral NBTXR3 on day 6. Secondary tumors in groups 4 and 5 were also irradiated with 1Gy x2 (LD-XRT) on days 12 and 13. Experimental groups were designated as 1 = Control, 2 = HD + IT, 3 = NBTXR3 + HD + IT, 4 = HD + LD + IT, and 5 = NBTXR3 + HD + LD + IT. The secondary tumors were analyzed by flow cytometry and Nanostring. On day 178, the survivor mice were rechallenged with 5 × 104 344SQR cells on the right flank and the tumor growth was monitored for an additional 36 days.

Results

All mice in all the groups except NBTXR3 + HD + LD + IT died due to the growth of either the primary tumor or the secondary tumor by day 36. Both the primary and the secondary tumors in 4 mice of NBTXR3 + HD + LD + IT group were completely eliminated. No tumor growth was observed in these mice after rechallenged with 344SQR cells. Flow cytometry data demonstrated that only the mice in the groups with NBTXR3 had significantly more CD8+ T cell infiltration in the secondary tumor collected on day 16 than the control. Both flow cytometry and Nanostring data showed that only the mice in NBTXR3 + HD + LD + IT had a significantly higher CD8+ T cell/Treg cell ratio than the control.

Conclusions

The combination of NBTXR3 plus high and low dose radiation with immunotherapy effectively controlled the growth of both primary and secondary tumors, significantly extended the survival, generating long-term antitumor memory. This combination therapy induced immune-mediated control of the secondary tumor at both genetic and cellular levels.

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References


In Vitro and in Vivo Combination Therapy of Low Molecular Weight Heparins, Chemotherapy and Immunotherapy, Induce Antitumor Activity in Pancreatic Cancer

Carboplatin, Paclitaxel and Pembrolizumab for the First Line Treatment of Recurrent and/or Metastatic Head and Neck Squamous Cell Carcinoma

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Background

A recent phase III study (Keynote-048) demonstrated survival benefit of platinum, 5-FU and pembrolizumab in 1st line treatment of recurrent and/or metastatic head and neck squamous cell carcinoma (RM-HNSCC). However, administration of 5-FU has been a challenge for logistics and toxicities. As platinum, paclitaxel and pembrolizumab has been shown to be an effective and safe treatment for non-small cell lung cancer, we hypothesized that carboplatin, paclitaxel and pembrolizumab would be safe and effective for 1st line treatment of RM-HNSCC.

Methods

We performed a retrospective study of RM-HNSCC patients who received carboplatin, paclitaxel and pembrolizumab for first line systemic therapy, treated between December 2015 and January 2020 at the University of California, San Francisco. Patients who received at least 1 cycle of treatment with pre-treatment and post-treatment images were included in the analyses. Response to the treatment was assessed using RECIST criteria version 1.1. We also estimated overall survival and progression free survival using Kaplan-Meier method.

Results

Nine patients who received carboplatin, paclitaxel and pembrolizumab as first line systemic therapy for RM-HNSCC were identified. Two patients had HPV positive oropharyngeal SCC, the other patients unknown primary SCC in head and neck (2), oral cavity SCC (2), laryngeal SCC (1), hypopharyngeal SCC (1) and SCC of orbit (1). There were 1 complete response (CR, 11%), 6 partial responses (PR, 55%), 1 stable disease (SD, 11%) and 1 progressive disease (PD, 11%). Overall response rate (ORR) was 78%, and median progression free survival and median overall survival have not reached with median follow-ups of 6 months and 8 months, respectively. Two patients discontinued chemotherapy after 1 cycle for grade 4 acute kidney injury and grade 4 anaphylaxis, yet achieved CR and PR, respectively.

Conclusions

The retrospective analysis suggests that first line carboplatin, paclitaxel and pembrolizumab for RM-HNSCC is an active regimen and can be considered in place of platinum, 5-FU and pembrolizumab, which merits further investigation.

Ethics Approval

The study was approved by UCSF’s Institutional Review Board, approval number 19-29363.
Methods BxPC-3, PANC-1, and MIA-PaCa2 were incubated alone or in combination with Tinzaparin (T) and/or Nab-Paclitaxel (A) and/or Gemcitabine (G) and/or Nivolumab (NI), Pembrolizumab (PE) and/or Iplilimumab (PI). The effect of these regimes on various signaling pathways controlling proliferation and apoptosis was identified in vitro through Western blot. Cell viability was measured with MTT assay. NOD/SCID mice will be used to generate xenografts with the PANC-1 cell line. Human peripheral blood mononuclear cells (PBMCs) from donors will be injected to give mice a human-like immune system.2

Results In a triple combinatorial scheme, N/E/P+I+P+T, the protein levels of VEGFR2 were decreased (0.1 to 0.7 folds) in a dose-dependent way in mtkRAS PC cell lines (PANC1 and MIAPAC2A). The number of PANC-1 cells was decreased around 40% in a triple combinatorial scheme of T+I+P+(NI or PE) after 48 hours. The triple combination of Gemcitabine + Nab-paclitaxel + Tinzaparin leads to a decrease in tumor size relative to control by 51% and relative to Nab-P + G by 15%. The combination of chemotherapy, immunotherapy, and Tinzaparin leads to a reduction in tumor size compared to control by up to 60%. Tinzaparin contributes an additional 20% Preliminary data show that the quadruple therapeutic regimen increases the percentage of CD8+ cells from 5% to 27% and decreases Tregs' percentage from 9.5% to 4% (in TILs).

Conclusions In vitro experiments show a decrease in the cell viability of PC cell lines and a reduction in the protein levels of VEGFR2 in mtkRAS cell lines. In vivo experiments with NOD/SCID mice and humanized NOD/SCID mice show a significant reduction in tumor volume in the combination therapy regimes with Tinzaparin. Possible mechanisms for these effects include an increase in CD8+ cells, a decrease in Tregs cells, a reduction in VEGFR-2 expression, and an increase in cancer cell apoptosis. This synergistic strategy can create new avenues for the treatment of patients with pancreatic cancer, achieving a better clinical outcome and greater survival.

REFERENCES


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PRECLINICAL CHARACTERIZATION AND DEVELOPMENT OF MG1124, A NOVEL IMMUNE CHECKPOINT INHIBITOR TARGETING CEACAM1 FOR NSCLC PATIENTS

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Background CEACAM1 is the only member of CEACAM family which is expressed on lymphocytes such as T cells and NK cells that mediate suppression of inflammatory T cell response. It is known that CEACAM1-CEACAM1 homophilic interaction induces downregulation of ZAP70 phosphorylation in response to T cell receptor (TCR) stimulation. There is a wealth of research demonstrating the correlation between CEACAM1 expression and cancer progression, in a wide range of indications. We developed a fully human monoclonal antibody (mAb) MG1124 that specifically binds to CEACAM1 but not to other CEA family members, thereby exerting antitumor effect via triggering immune response.

Methods T cell activation of MG1124 was determined by an NFAT-luciferase reporter assay with CEACAM1 overexpressing Jurkat stable cells. In vitro efficacy of MG1124 alone or in combination was studied in a humanized mouse model. As MG1124 binds to monkey CEACAM1 with high affinity, pharmacokinetics assessment of MG1124 was performed in cynomolgus monkeys.

Results An anti-CEACAM1 antibody MG1124 bound to CEACAM1 but not to other CEA family members. MG1124 blocked CEACAM1 homophilic interaction by binding to the N domain of CEACAM1. Especially the homophilic interaction induced downregulation of ZAP70 phosphorylation in response to TCR stimulation in a CEACAM1 overexpressing Jurkat stable cell line, which was rescued by MG1124 resulting in augmentation of NFAT activity and IL-2 expression. NK cell or cytotoxic T cell-mediated tumor lysis was increased by MG1124 in a CEACAM1 expression-dependent manner. MG1124 inhibited tumor growth in CEACAM1 expressing NSCLC DXD humanized mouse models. In an NSCLC PDX humanized mouse model, MG1124 dose-dependently inhibited tumor growth as monotherapy. Moreover, MG1124 showed synergistic anti-cancer activity with pembrolizumab in NSCLC hPDX models. Pharmacokinetic (PK) analysis in cynomolgus monkeys showed that the half-life (T1/2) of MG1124 was estimated to range from 14 to 17 days, and the peak plasma concentration (Cmax) and overall exposure (AUC) were found to be generally dose proportional. Following this PK study, a toxicity study in cynomolgus monkeys is ongoing.

Conclusions MG1124, a novel anti-CEACAM1 mAb, blocked CEACAM1-mediated negative regulation and restored NK or cytotoxic T cell activities. MG1124 showed effective anti-tumor activity in vivo mouse models and its combination with PD-1 blockade further enhanced treatment efficacy. The data presented herein support further advancement of MG1124 towards clinical development. MG1124 is a potential therapeutic candidate for immune checkpoint blockade in cancer therapy.

REFERENCES


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THE ROLE OF IMMUNE CHECKPOINT INHIBITOR AS A SINGLE AGENT OR COMBINATION THERAPY IN ADVANCED THYROID CANCER

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Background There is a high unmet need for effective systemic treatment for patients with metastatic radioactive iodine