Radiosensitization of Adenoid Cystic Carcinoma with MDM2 Inhibition

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Abstract

Purpose: Adenoid cystic carcinoma (ACC) is a rare cancer arising from the major or minor salivary gland tissues of the head and neck. There are currently no approved systemic agents or known radiosensitizers for ACC. Unlike the more common head and neck squamous cell carcinomas that frequently harbor TP53 mutations, ACCs contain TP53 mutations at a rate of <5%, rendering them an attractive target for MDM2 inhibition.

Experimental Design: We report the successful establishment and detailed characterization of a TP53-WT ACC patient-derived xenograft (PDX), which retained the histologic features of the original patient tumor. We evaluated this model for response to the MDM2 inhibitor AMG 232 as monotherapy and in combination with radiotherapy.

Results: AMG 232 monotherapy induced modest tumor growth inhibition, and radiation monotherapy induced a transient tumor growth delay in a dose-dependent fashion. Strikingly, combination treatment of AMG 232 with radiotherapy (including low-dose radiotherapy of 2 Gy/fraction) induced dramatic tumor response and high local tumor control rates 3 months following treatment. Posttreatment analysis revealed that although both AMG 232 and radiotherapy alone induced TP53 tumor-suppressive activities, combination therapy amplified this response with potent induction of apoptosis after combination treatment.

Conclusions: These data identify that MDM2 inhibition can provide potent radiosensitization in TP53-WT ACC. In light of the absence of effective systemic agents for ACC, the powerful response profile observed here suggests that clinical trial evaluation of this drug/radiotherapy combination may be warranted to improve local control in this challenging malignancy.

Introduction

Malignancies of the salivary glands are a relatively rare and diverse group of tumors, accounting for roughly 3% of all head and neck cancers (1). Adenoid cystic carcinoma (ACC) comprises approximately 10% of salivary gland tumors and is characterized by a generally slow but unpredictable growth rate and a high rate of eventual local and distant metastasis (1). These tumors are categorized histologically as solid, tubular, or cribriform patterns, with the solid form typically demonstrating more aggressive disease than the other types (2–6). Despite modern surgical treatments for patients with newly diagnosed ACC, both local and distant recurrences remain common, highlighting the need for improved therapy options (7). Despite dozens of clinical trials examining drug therapies, there are no FDA-approved systemic agents for ACC, with conventional and molecular therapeutics eliciting crude response rates typically less than 10% to 20% (8–15). The most widely utilized regimen of cisplatin plus vinorelbine has significant toxicities and a modestly higher response rate (16). The current standard of care remains surgical resection and postoperative radiotherapy (1, 8), however, with a high propensity for local and distant failure. The addition of cisplatin to adjuvant radiotherapy is currently being investigated in a randomized RTOG study enrolling multiple salivary gland histologies including ACC, but these results are not anticipated for several years.

The hallmark tumor suppressor protein p53 is a transcription factor that regulates cell-cycle progression, senescence, DNA repair, and apoptosis to control tumor cell growth (17). TP53 is mutated in roughly 50% of all tumors (18, 19), but the majority of ACCs express wild-type (WT) p53. This is in stark contrast to head and neck squamous cell carcinoma in which TP53 mutations are seen in over 50% of cases. In ACC, TP53 mutations have been identified in approximately 5% of cases (20, 21). p53 protein levels are regulated by MDM2, an E3 ubiquitin ligase, which...
targets p53 for proteasomal degradation (22). MDM2 inhibitors are known to exhibit antitumor effects and are currently being studied in clinical trials (23–25). In ACC, the promising efficacy of an MDM2 inhibitor alone or in combination with cisplatin has recently been demonstrated in the treatment of ACC patient-derived xenografts (PDX; refs. 26, 27). In this study, we investigated the radiosensitizing effect of AMG 232, a picomolar affinity piperidinone inhibitor of MDM2 that is currently in clinical trials for several tumor types. AMG 232 appears to synergize with p53-activating therapies, such as DNA-damaging agents, likely potentiating p53 signaling, leading to increased apoptosis and decreased cell proliferation (28–30).

Among many antitumor effects, ionizing radiotherapy activates p53 to induce its array of tumor-suppressive functions. AMG 232 and other MDM2 inhibitors have been shown to radiosensitize non–small cell lung cancer, breast cancer, colon cancer, melanoma, and prostate cancer cell lines that are p53 WT, with more modest efficacy in models that harbor p53 mutations (31, 32). Given the low rate of TP53 mutation in ACC and promising preclinical data demonstrating a role for MDM2 inhibition in ACC, we hypothesized that the combination of AMG 232 and radiotherapy would result in improved tumor control than either treatment alone. Herein, we describe the characterization of an ACC PDX model, the potent radiosensitizing effect of AMG 232 on this tumor, and analysis investigating molecular mechanisms underlying this radiosensitization.

**Materials and Methods**

**Mice**

Six- to 8-week-old female NOD/SCID gamma (NSG, NOD. Cg-Prkdcscid Il2rgtm1Wjl/Sigl) mice (The Jackson Laboratory) were used for PDX establishment and tissue amplification. Six- to 8-week-old female Hsd: athymic Nude-F1™ (Harlan Laboratories) mice were used for therapy studies. Mice were kept in the Association for Assessment and Accreditation of Laboratory Animal Care–approved Wisconsin Institute for Medical Research Animal Care Facility, housed in specific pathogen-free rooms and had their clinical health evaluated at least twice weekly. All studies involving mice were carried out in accordance with a University of Wisconsin Institutional Animal Care and Use Committee–approved protocol.

**PDX propagation and tumor harvesting**

The UW-ACC-60 PDX was established and propagated as described previously for head and neck squamous cell carcinomas (33, 34). TP53 sequencing was performed on total genomic DNA using the Illumina TruSeq Cancer Amplicon panel and has been deposited with the sequence read archive under BioProject ID: PRJNA381909.

**Genetic testing of ACC PDX and patient donor tumor**

The identity of the first and fifth passages of the ACC PDX was confirmed to match its original patient donor tumor via short tandem repeat (STR) testing. Total genomic DNA was isolated from flash-frozen tissue for all instances of the tumor using the Qiagen DNeasy kit. An 18 loci STR assay (Promega PowerPlex 16 HS System #DC2100) was performed by the UW Translational Initiatives in Pathology CORE facility. The same DNA samples were used to test for presence of the MYB-NFIB gene fusion frequently detected in ACC via a PCR-based approach (35) using the following primer sets: MYB-1910F 5′-AGCTCGCGTTTGAATGGC-3′; NFIB-1096R 5′-GGTTTAAATGGGTGTCCTA-3′;

**Radiation in ACC**

Go reirradiation for palliation. Here, we demonstrate robust tumor regression by treatment of ACC patients with AMG 232 and radiation.
Statistical analysis of PDX treatment study

A one-way ANOVA model was utilized, with the null hypothesis that the group means of control, AMG, AMG + 2 Gy, AMG + 5 Gy, and AMG + 8 Gy are equal and was tested globally. We investigated how well the model fit the data by reporting goodness-of-fit statistics, including R-squared measures, which describe the percentage of variation in the response explained by the model. Finally, we performed post hoc analysis to assess the effects of pairwise comparisons between the groups (i.e., AMG vs. control, AMG vs. AMG + 2 Gy, AMG vs. AMG + 5 Gy, AMG vs. AMG + 8 Gy), using Tukey honestly significant difference post hoc test. All statistical analyses were performed using the two-sided alpha level of 0.05, with STATATA v14 software.

The dose of radiotherapy required to result in 50% tumor control (TCD50) was calculated at day 125. The proportion of injection sites with no palpable tumor (tumor volume = 0) was calculated. The confidence intervals of the proportion were used to set the range, the radiotherapy dose was converted to log10 format, and the resulting data points fit to a log(treatment) versus response curve using a least squares fit. The log(TCD50) was compared by the extra sum-of-squares F test using GraphPad Prism v7.0a.

To assess antagonistic, additive, or synergistic effects, we used the fractional product method as described previously (37) one week after the end of treatment. Briefly, the observed fractional tumor volume (FTV) is equal to the mean tumor volume of each treated group (AMG 232, radiation, or AMG 232 + radiation) divided by the mean tumor volume of the control group. The expected FTV from the combined treatment (FTVAMG 232 + radiation) is calculated by multiplying the observed FTVAMG 232 by the observed FTVradiation. Dividing the expected FTVAMG 232 + radiation by the observed FTVAMG 232 + radiation yields a synergy assessment ratio in which a value >1 suggests that the combined treatments are effectively synergistic, <1 antagonistic, and =1 additive.

Histology and IHC

Hematoxylin and eosin (H&E) staining was used for formal pathologic analysis and to assess tumor quality. Additional slides were processed by the UW Translational Research in Pathology lab to assess expression of p63, CD117, and CK5/6 by IHC. Staining for expression of p53, p-p53, and Ki-67 was performed by standard IHC techniques as described previously (12, 38). See Supplementary Table S1 for reagent details. A no primary antibody control slide was stained with each condition to ensure appropriate) near infrared–conjugated secondary antibodies (LiCOR), and imaged on a LiCOR Odyssey FC. Antibodies and sources are listed in Supplementary Table S1.

In situ hybridization by RNAscope

RNA levels were examined using the RNAscope 2.5 HD Detection Reagent – Brown (Advanced Cell Diagnostics) according to the manufacturer’s protocol. Slides were baked at 60 °C for an hour and then deparaffinized by incubating in xylene twice for 5 minutes. Slides were then treated in 100% ethanol twice, for 1 minute each, at room temperature, and then air dried. Heat antigen retrieval was carried out using RNAscope 1× Target Retrieval Reagents. RNAscope hydrogen peroxide was added to the tissue sections, and the slides were incubated for 10 minutes and dried. Slides were then baked in the HybEZ Oven at 40 °C for 30 minutes. After baking, the Hs-CDKN1A hybridization probe (ACD 311401) was applied to the slides and incubated in the HybEZ oven for 2 hours at 40 °C. The probe was followed by the application of Hybridization Amps 1–6. Slides were washed between the application of the probe and amps using 1× RNA-scope wash buffer. Signal detection was carried out using DAB; slides were counterstained using 50% hematoxylin, and washed with 0.02% ammonia water. Slides were then dehydrated using 70% ethanol, 95% ethanol (2×), incubated in xylene for 5 minutes, and then coverslipped using Cytoseal XYL (Thermo Fisher Scientific) and a number 1.5 coverslip.

Apoptotic body count

The xenograft specimens were fixed in 10% buffered formalin and processed for routine paraffin sections. The 5-μm sections were stained by hematoxylin and eosin. The number of apoptotic bodies per field was counted with a 60× objective and 10× eyepiece under light microscopy on hematoxylin and eosin–stained slides by a blinded pathologist (R. Hu). Areas adjacent to necrosis were avoided. Apoptotic bodies were identified as shrunken cells with compact, segregated and sharply delineated chromatin with a deeply cosinophilic cytoplasm. Five to 10 random fields were examined in each specimen depending on the size of tissue, and average was taken to represent the count for each condition.

Results

Establishment and characterization of ACC PDX

The PDX was established in NSG mice from a portion of a surgical specimen from a patient with a regional recurrence of xylene and coverslipped with Cytoseal XYL (Thermo Fisher Scientific) and a number 1.5 coverslip. Where conducted, positive cell counts were performed using ImageJ with statistical analysis using GraphPad Prism. Semi quantitative analysis of IHC staining intensity was performed using ImageJ with the Colour Deconvolution plugin.
Figure 1.
Characterization of ACC PDX. A, H&E and IHC staining of the primary patient tumor, the first passage PDX, and the most recent (fifth passage) PDX. IHC diagnostic markers for ACC included CD117, stains the luminal lining cells but not abluminal cells; p63 stains the abluminal cells only; CK5/6 stains abluminal cells weakly and stains luminal epithelium strongly. B, Left, summary of nonsynonymous mutations identified by hotspot sequencing. Green, no oncogenic mutations identified; red, potentially oncogenic mutation identified. Right, coverage map of TP53 sequencing. Gray bars are histogram of counts for each target amplicon. Orange bars are TP53 coding DNA sequence, with intervening noncoding regions indicated by dashed line. Blue boxes are target amplicons included in the sequencing panel.
Figure 2.
Radiotherapy and AMG 232 combination therapy of ACC PDX. A, Growth curves representing tumor volume of the 8 treatment groups as a function of days postengraftment. Filled symbols represent mock/radiotherapy only groups; open symbols are AMG 232/radiotherapy combination groups. Radiotherapy fractions were delivered on days indicated by inverted triangles. AMG 232 or vehicle was delivered by oral gavage once per day over time period shown.

B, TCD50 analysis of ACC PDX ± AMG 232; AMG 232 tumor control, mice were followed over 100 days after the end of treatment, and still, no tumor regrowth was observed. Animals treated with either 5 or 8 Gy/fraction demonstrated more rapid tumor shrinkage and also had no apparent tumor regrowth at the end of the study.

Statistical analysis was performed to determine whether increased radiotherapy dose produced an antitumor benefit. One-way ANOVA model was conducted to determine whether the mean volumes were different between five treatment groups: control, AMG 232, AMG 232 + 2 Gy, AMG 232 + 5 Gy, and AMG 232 + 8 Gy. There was a statistically significant difference between groups as determined by ANOVA (F(4,45) = 14.47, P < 0.0001), with approximately 56% of the variance being explained by the model. In addition, a Tukey post hoc test shows that mean scores were significantly lower in AMG 2 Gy group compared with AMG alone group [−0.657.54 ± 160.118 (SD), P = 0.002]. Similarly, a statistically significant difference revealed a lower mean score for all the combination therapy groups compared with either the control or AMG 232 only groups. However, there was no statistically significant difference between AMG + 2 Gy versus AMG + 5 Gy (P = 0.998) or AMG + 5 Gy versus AMG + 8 Gy (P = 0.999). These data suggest that increasing doses from 2 to 8 Gy within the combination arms were not statistically different from each other. To further assess the ability of AMG 232 to improve tumor control, a TCD50 calculation was performed (Fig. 2B). Radiotherapy alone failed to control any tumors (TCD50 > 8 Gy/fraction), while combination with AMG 232 significantly decreased the TCD50 (<0.6 Gy/fraction, P < 0.0001) consistent with radiosensitization. We used the fractional product methods to calculate a synergy assessment ratio for AMG 232 and each radiation dose. The ratio’s calculated (2.1, 3.2, and 3.3 for 2, 5, and 8 Gy, respectively) are consistent with a finding of synergy between radiation and AMG 232.

Radiotherapy and AMG 232 activate p53 and downstream signaling

We next investigated the molecular response to this treatment regimen. The effect on p53 and p-p53 levels was examined by Western blotting and IHC on xenograft tissues harvested 2 hours posttreatment. Total p53 levels were fairly stable with some increase at higher radiotherapy doses, while both AMG 232 or radiotherapy alone did activate p53 as shown by higher p-p53 levels. The combination of radiotherapy and AMG 232 showed increased p53 and p-p53 activation relative to radiotherapy or AMG 232 alone (Fig. 3A and B). Semiquantitative analysis of the IHC images confirmed increased p53 and p-p53 activation in treated tumors (Supplementary Fig. S3). DNA damage was detected by immunoblot for γ-H2AX and KI80 2 hours postradiotherapy; expression of γ-H2AX was radiotherapy dose dependent, but the addition of AMG 232 had no effect. Little effect on KI80 was observed. Tumor samples harvested 48 hours posttreatment revealed that AMG 232 treatment promoted elevated levels of MDM2 consistent with feedback that is typical after prolonged exposure to an inhibitor, with elevated levels of the P53 effector protein PUMA observed in all treated tumors (Fig. 3A).

Downstream effects of p53 activation were evaluated by CDKN1A response (Fig. 3C). At 2 hours posttreatment, elevated CDKN1A RNA was identified by in situ hybridization (RNAscope) in both the AMG 232 and radiotherapy single modality
treatments with the combination presenting even greater expression. This effect was confirmed at the protein level where the combination produced elevated CDKN1A as seen by IHC. Semi-quantitative analysis of the IHC images showed a dose-dependent elevation of CDKN1A with increasing radiation (Supplementary Fig. S3). Together, the results confirmed that the treatment regimen was inducing expected DNA damage and TP53-mediated tumor-suppressive pathways.

Radiotherapy and AMG 232 cooperatively induce antiproliferative and proapoptotic responses

We next evaluated the growth and cell death impact of these treatments on the ACC PDX. Using tumor tissue harvested 48 hours after a single dose of drug and/or radiotherapy, we immunostained for the proliferation marker Ki-67 and counted positive nuclei from multiple fields for each condition (Fig. 4A). Relative to mock-treated animals, all treatments reduced cell proliferation, with a greater reduction and higher level of significance for the high dose radiotherapy + AMG 232 combination. We next immunostained for cleaved caspase-3, a marker of early stages of apoptosis, in tumors 48 hours after re-treatment with a single dose of AMG 232 or radiotherapy (Fig. 4B). On the basis of counting of cleaved caspase-3–positive nuclei, neither AMG 232 nor 2 Gy radiotherapy alone increased apoptosis in these tissues. Although the 8 Gy fraction did have higher counts, it did not reach statistical significance. Consistent with the rapid shrinkage of the tumors in the AMG 232 + radiotherapy arms, both of these treatments presented significantly elevated caspase staining in a dose-dependent manner. We analyzed later stages of apoptosis by counting apoptotic bodies in multiple high-power fields for the same samples. In this analysis, only the AMG 232 + 2 Gy treatment produced a statically significant increase in apoptosis, with the AMG 232 + 2 Gy counts slightly elevated after this single fraction (Fig. 4C). Overall, these results are consistent with an antiproliferative, growth-delay impact of the AMG 232 and...
Figure 4.
Proliferation and apoptosis markers following radiotherapy and AMG 232 treatment. A, Ki-67 immunostaining of PDX samples harvested 48 hours posttreatment. Images are representative of 20× fields; scale bars, 10 μm. Treatment was scored by counting Ki-67–positive nuclei from three 20× fields per condition. Bar plots, mean counts with SD; statistical analysis by one-way ANOVA with Tukey multiple comparisons. B, Cleaved caspase-3 staining and quantification of 48-hour posttreatment tumor samples. Images are representative of 40× fields; scale bars, 20 μm. Cleaved caspase-3–positive nuclei within the tumor were counted for three 40× fields for duplicate tumor samples; stromal regions were ignored. Cells presenting cytoplasmic or background staining were not included in counts. Bars are mean of all fields scored for a given condition with SD; statistical analysis by one-way ANOVA with Tukey multiple comparisons. C, Quantification of apoptotic bodies in 48-hour posttreatment tumor samples in H&E-stained slides. Five to ten 60× fields were counted for duplicate tumor samples. Representative images are shown for mock and AMG 232 + 8 Gy treatments (scale bars, 20 μm) with inset images with arrows highlighting apoptotic bodies (scale bars, 5 μm). Bars are mean of all fields scored for a given condition with SD; statistical analysis by one-way ANOVA with Tukey multiple comparisons. * * * * , P < 0.0001; ** , P < 0.01; *, P < 0.05.
radiotherapy single-modality treatments, but a cell death-inducing, tumor-shrinking effect of the combination.

Discussion

ACC patients have limited treatment options beyond surgery and radiotherapy, and long-term prognosis remains poor. There is a need for novel therapeutic options to improve care, particularly for patients with metastatic disease. The rarity of the disease, the lack of robust preclinical models, and the absence of effective systemic therapies to date remains a major challenge for ACC patients. We developed and characterized a PDX model (UW-ACC-60) representing one of only a handful available for sustained preclinical investigation of ACC (27, 40). This model represents the most prevalent type of ACC seen in patients, the cribriform subtype and maintains its histologic features over multiple passages.

Targeted sequencing demonstrated that this model, like the majority of ACCs, does not contain a TP53 function altering mutation, making it amenable for treatment approaches that rely on functional p53. The low rate of TP53 mutations seen in ACC has led other groups to investigate the efficacy of MDM2 inhibitors as potential systemic therapies given alone, or in combination with cisplatin. Nor and colleagues used PDXs established at their institution to demonstrate that an MDM2 inhibitor, MI-773, slowed growth of ACC both alone and when combined with cisplatin (26, 27). They showed that MDM2 inhibition led to p53 activation, induction of apoptosis, tumor growth delay, and could prevent the recurrence of surgically resected xenografted tumors.

On the basis of the critical need for innovative approaches to improve local control for patients both newly diagnosed with ACC and dealing with local–regional recurrences, we began this project to investigate potential radiosensitizers of ACC. Building on the work by Nor and colleagues (26, 27), and our success using AMG 232 to radiosensitize lung squamous cell carcinoma in addition to cell lines derived from colon, breast, sarcoma, and melanoma (31), we combined AMG 232 with radiotherapy in ACC. We hypothesized that radiation-induced p53 activity would be enhanced by inhibiting MDM2, a negative regulator of p53. This combination would thus take advantage of the low rate of TP53 mutation seen in ACC. The combination of radiotherapy and AMG 232 resulted not only in growth delay typically seen in xenograft studies, but also complete regression of the tumors that persisted for months after the conclusion of treatment. Although both MDM2 inhibition or radiotherapy alone were sufficient to activate p53 signaling, as single modalities, they had modest effects on tumor growth. Combination treatment decreased Ki-67 staining and induced apoptosis consistent with not only growth delay but also the observed tumor regression. AMG 232 + radiotherapy resulted in greater p53 pathway induction than either treatment alone as demonstrated by upregulation of p53 target genes and increased protein expression. Given the key role of p53 as a tumor suppressor, these findings are not unexpected and in fact complement what both we, and Nor and colleagues, have previously demonstrated regarding the mechanism of MDM2 inhibition as an anticancer therapy.

Radiosensitization and xenograft cures were observed with total radiotherapy doses as low as 16 Gy delivered over 4 weeks. Although additional studies confirming the efficacy of AMG 232 in combination with low-dose radiotherapy would be needed, these results are encouraging. Many ACC patients live years after completion of adjuvant radiotherapy and often are faced with the difficult decision to undergo repeated operations and/or reirradiation due to local and/or regional tumor progression. This work raises the possibility that a radiosensitizer could be combined with focal radiation to improve local tumor control. Using modern techniques, highly conformal radiation can be easily delivered to sites of measurable disease while limiting the volume of normal tissues receiving appreciable radiotherapy dose. Although this combination would need to be carefully studied to ensure reasonable normal tissue toxicity, we did not identify any significant toxicity in the mice treated with combination therapy.

We acknowledge several limitations of this study. As with most current PDX studies, we completed these experiments in immunocompromised animals, thus limiting our ability to identify immunologic mechanisms, and focused the study on intrinsic radiosensitivity. It is possible that the addition of immune-mediated cell death driven by radiotherapy and AMG 232 would require even lower doses to achieve similar results. Although there are several other described ACC PDX models (27, 28), the studies in this article clearly utilize only a single in vivo model developed from a single patient. The fact that the histology of this model (cribriform subtype) is the most common type of ACC and that the mutational profile is consistent with recently published sequencing of ACC patients suggests that these results may have more broad implications, but additional work is needed to confirm these findings. Finally, because no ACC-immortalized cell lines are publicly available (41), and we have thus far been unable to establish a reliable in vitro model, our experiments were limited to in vivo studies. We have an active tissue donation protocol ongoing and are seeking to generate additional PDXs and derive cell lines or 3D culture models of ACC to further these and future investigations.

In conclusion, we have demonstrated robust radiosensitization of an ACC PDX by combining the MDM2 inhibitor AMG 232 with relatively low doses of radiotherapy. Physicians who care for ACC patients know all too well the desperate need for both new systemic agents as well as improved local control for these patients. Given the low frequency of TP53 mutation in ACC, tumor characterization or patient selection criteria to identify patients with wild-type TP53 may be unnecessary for a clinical trial. This work adds to the growing evidence that targeting MDM2, alone or in combination with another anticancer therapy, in patients with ACC may be a successful treatment strategy. Through continued work, we may yet be able to improve quality of life, and potentially improve survival, in patients living with ACC.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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