Paper # 2024

SIGNIFICANCE OF THE INSURANCE AUTHORIZATION SYSTEM & THE IMPACT ON A HEMATOLOGY ONCOLOGY SERVICE

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Background: Limited data exists on prior authorizations (PAs) and the impact on medical care for pediatric patients as compared to adults. The PA process not only impacts patients financially but also health-care systems. It is estimated that $631 million a year is spent on PAs. The purpose of this study is to evaluate the PA process. Pediatric oncology patients, in particular, require strict treatment adherence as it is crucial for survival.

Objectives: To evaluate the frequency of PAs completed, non-physician time spent completing PAs, frequency of PAs requiring peer-to-peer evaluation, estimated cost for non-physician/physician time spent on completing PAs, and number of PAs resulting in delay of medical care.

Design/Method: A prospective study evaluating PA requests of pediatric patients (0-28 yrs.) followed in the hematology oncology division at our institution for either a hematology and/or oncology diagnosis over 6 months (August 2021 to February 2022). A PA form, as standard of care, was created to ensure appropriate documentation. The PA form was completed by the department's insurance coordinator and/or the physician who completed a peer-to-peer evaluation. A preliminary analysis of data was performed with final analysis to be completed in February of 2022.

Results: A total of 111 PAs were completed at the time of the analysis. Non-chemotherapy medications were the most frequent PAs (52/119) followed by chemotherapy (44/119). The median time (min.) for non-physician completion of medication PAs was 50 min. The total non-physician time spent to complete 111 PAs was 109 hours. The total non-physician cost was $1 847.27. Of the cohort, 97 PAs (87%) were approved, whereas 14 (13%) were declined. Of the PAs declined, 8 (57%) required peer-to-peer evaluation. All peer-to-peer evaluators were non-pediatric trained (100%). The mean physician time spent completing a peer-to-peer was 16 min. The total physician cost was $232.21. Two PAs were denied after peer-to-peer evaluation (25%), resulting in delay of medical care. Change in clinical management occurred in 4 patients (29%). One limitation included imaging PAs that were completed as per a separate hospital protocol. We suspect denial in PAs would have been more robust if imaging was included.

Conclusion: PAs require a significant time spent by non-physician staff. A non-pediatric trained physician can impact a decision resulting in delay of medical care, overall impacting the morbidity of a pediatric patient. In a small cancer center similar to ours with on average 40 new diagnoses/year, a change in clinical management occurring 20% of the time is significant.

Paper # 2025

TARGETING CD70 USING CAR-NK CELLS TO ENHANCE NK CELLS CYTOLYTIC EFFECT AGAINST OSTEOSARCOMA

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Background: Osteosarcoma (OS) is the most common primary malignant bone tumor among pediatric patients. Effective chemotherapy regimens for refractory OS are scarce, accounting for no improvements in patient survival. Therefore, novel therapies are needed. Although our understanding of the antigenic landscape of OS is nascent, emerging knowledge suggests that CD70 is a viable candidate. CD70 is a transmembrane protein that activates T cells and is hypothesized to cause T-cell exhaustion in solid tumors. CD70 is expressed in primary OS bone tumors with higher expression in lung metastases, the main cause of death in these patients. Pre-clinical studies using an anti-CD70 antibody (ARGX-110) demonstrated indirect anti-tumor effects mediated by NK cells. We hypothesize that direct tumor antigen targeting using specific chimeric antigen receptor (CAR)-Natural Killer (NK) cells directed against CD70 could improve NK cell cytolytic activity against OS.

Objectives: To evaluate if CD70 directed CAR-NK cells will enhance the therapeutic effect of adoptive transferred NK cells against OS.

Design/Method: Analysis of the cBioportal database (https://www.cbioportal.org) confirmed CD70 expression in OS. Flow cytometry was used to determine surface expression of CD70 on several human OS cell lines (SJSA, OS-17, LM7, CCH-OS-D) and normal human osteoblasts. CD70 CAR constructs were sequenced, verified and transduced into NK cells by collaborators. CD70 CAR-NK cells cytolytic activity against OS-17 cells as compared to NK cells was evaluated by incubating the CD70 CAR-NK cells with OS-17 cells at various effector to target (E:T) ratios. *In vitro* cytokine release was measured upon CD70 CAR-NK cells exposure to OS cells (IsoPlexis).

Results: Database analysis confirmed CD70 gene amplification in sarcomas including OS as compared to other tumors. Flow cytometry demonstrated variable expression of CD70 (MFI) on OS cells and no CD70 expression on human osteoblasts. The cytotoxicity assay revealed an increase in percent lysis at the highest E:T ratios compared to control NK cells. Higher CD70 expression did not correlate with increased cytolysis as cytolysis of CCH-OS-D (lowest CD70 expression) was also achieved. We found a predominant release in the MIP-1a, MIP-1b, and IFN-g cytokines upon OS-17 exposure to CD70 CAR-NK cells.

Conclusion: CD70 is an attractive target with immunotherapy potential against OS. We showed that CD70-CAR NK cells are effective against OS cells *in vitro* compared to control NK cells. CD70-CAR NK killing does not correlate with an increased level of CD70 expression. Increased MIP-1a, MIP-1b, and IFN-g suggest increased CD70-CAR NK cells effector activity and may

explain the increased cytolytic effect.

Paper # 2026

COMBINATION AURORA KINASE A AND CDK2 INHIBITION IN RHABDOMYOSARCOMA

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Background: Rhabdomyosarcoma (RMS) is an aggressive childhood cancer for which new therapies are needed. The cyclin-dependent kinases CDK4 and CDK2 regulate cell cycle progression, and are frequently activated and/or overexpressed in RMS. Aurora Kinase A (AURKA) is a cell cycle kinase important in mitosis and cytokinesis, and is overexpressed in RMS. Inhibition of AURKA has been reported to induce cancer cell senescence and polyploidy.

Objectives: We hypothesized that combined inhibition of CDK2/CDK4 and AURKA will be effective in tumor suppression of RMS cells and more effective than either agents alone.

Design/Method: We used the human RMS cell lines, RD and Rh30, and their derived xenografts in immunocompromised NOD-SCID mice, to evaluate the effects of kinase inhibition on RMS cell proliferation, apoptosis, and tumor growth. We also investigated pathways potentially contributing to the drug effects through protein analysis.

Results: Dual inhibition of CDK2 and CDK4 in RMS cell lines showed a significant effect on increased RMS cell death, decreased progression through S-phase, and increased senescence markers. AURKA inhibition also significantly inhibited RMS cell proliferation, and resulted in a increase in polyploid cells. However, this effect was partially alleviated in combination therapy using CDK2/CDK4/AURKA triple inhibition. We therefore reasoned that inhibition of CDK4 may be arresting cells in G1, protecting them from effects of AURKA inhibition. Indeed, reverting to a dual combination of AURKA inhibitor and CDK2 inhibitor alone, we observed a significant effect on cell proliferation arrest and cell senescence. Combination CDK2/AURKA inhibition led to persistent effects on cell numbers, with more effective inhibition of tumor cell survival even after withdrawal of treatment. Dual combination inhibition led to less polyploid cells as compared to AURKA inhibition alone, and arrest of cells in G2/M to a higher extent that with either agent alone. Western blot analysis showed that, as expected, AURKA inhibition increased Cyclin B2 and p21 levels, demonstrating cell cycle arrest in mitosis. Treatment of mice bearing rhabdomyosarcoma xenografts showed significantly improved tumor control in mice treated with the dual combination, comapred to either agent alone. No excess toxicity was observed *in vivo* using dual inhibition.

Conclusion: Utilizing preclinical tumor models, we show that dual CDK2 and AURKA inhibition was more effective than either drug alone in treating RMS tumor cells, both *in vitro* and *in vivo*. Further work is ongoing to validate these combinatory targets in additional preclinical RMS models, and assess downstream pathways impacted by treatment.

Paper # 2027

INCREASED MORBIDITY IS ASSOCIATED WITH INITIAL PARTIAL SHAVE BIOPSY OF PEDIATRIC MELANOCYTIC TUMORS

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Background: Pediatric melanoma accounts for 2-3% of pediatric cancer and is the most common form of skin cancer in children. Appropriate treatment of localized melanoma relies on accurate staging which is largely based on the Breslow thickness of the primary tumor. Although the American Academy of Dermatology recommends excisional biopsy for suspicious skin lesions, partial shave biopsies are often performed in children. Shave biopsies can transect the base of a melanocytic tumor, negatively impacting accurate microstaging, prognostic evaluation, and therapy planning.

Objectives: Evaluate diagnostic biopsy methods in patients with cutaneous melanocytic lesions and their impact on staging, diagnosis, and treatment.

Design/Method: Retrospective analysis of pediatric patients treated for cutaneous melanocytic lesions from 2014 to 2021 at the University of Pittsburgh Medical Center. Variables included patient demographics, biopsy method, presence of positive deep/lateral margins, compromise of microstaging, extension of wide local excision or sentinel lymph node biopsy, need for skin graft, and final diagnosis.

Results: Data was analyzed for 103 patients with lesions that ranged from atypical with unknown malignant potential to melanoma. Of the 103 patients, 55 were female and 48 male with an age range of 1-22. Shave biopsy was performed in 66% of patients, punch in 19%, excisional in 14% and snip in 1%. Of all patients with positive margins, 75% had a positive deep margin and 92% of those patients had an initial shave biopsy. In patients with compromised microstaging due to positive deep margin, 89% had shave biopsy compared to 0% in punch. Twelve patients underwent a larger wide local excision of the primary tumor and seven had sentinel lymph node biopsy due to compromised microstaging, all underwent shave biopsies. Three out of 12 patients with larger excisions required a skin graft and hospital admission. Of patients who had a shave biopsy with compromised microstaging, 44% had a final diagnosis of melanoma compared to 33% in excisional and 0% in punch.

Conclusion: Pediatric patients with suspicious cutaneous melanocytic lesions frequently had shave biopsy as their initial diagnostic evaluation. There was a higher incidence of positive deep margins and compromised microstaging after shave biopsy compared to alternative methods. Increased morbidity associated with definitive surgical management was observed only in the shave biopsy group, including larger wide local re-excisions, skin grafts, hospital admission, and sentinel lymph node biopsy. These findings suggest that patients with shave biopsy had a higher

incidence of altered care due to compromised microstaging requiring more invasive surgical treatment.