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TITLE: Clonal Hematopoiesis as a Determinant for Bone Marrow Toxicities for Targeted Radiation Therapies in Prostate Cancer

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14. ABSTRACT

Targeted radionuclide therapy (TRT) is an emerging therapy in prostate cancer (PC), with PSMA-TRT showing a survival advantage with near-term approval for 177Lu-PSMA-617 expected and trials activated in earlier disease states. While most patients tolerate treatment, myelosuppression to varying degrees is one of the common toxicities and there is a risk of long-term bone marrow toxicity due to radiation. Identification of patients that are predicted to have short- and long-term toxicities from TRT is of major clinical interest. Clonal Hematopoiesis (CH) is aging related and is associated with smoking and previous exposure to radiation/chemotherapy. Our long-term goal is to identify CH signatures that predict short term and long-term bone marrow toxicities from TRT. Our *hypothesis* is that CH mutations have variable penetration based on specific PC therapies (especially TRT) and impact incidence of cytopenias and future risk of MDS/AML.We will utilize samples collected retrospectively and prospectively to: (1) Determine the prevalence of pre and post treatment cytopenias in patients with and without CH (2) Compare longitudinal behavior of individual CH mutations, including those known to impact future risk of MDS and (3) Contrast post treatment CH signatures in TRT patients with non-TRT treated patients.

15. SUBJECT TERMS None listed.					
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1. INTRODUCTION

BACKGROUND: Targeted radionuclide therapy (TRT), particularly when directed at prostate-specific membrane antigen (PSMA) is an emerging therapy in prostate cancer that has recently shown improvements in nearly all clinical trial endpoints in patients with late stage metastatic castration-resistant PC (mCRPC). While most patients tolerate treatment, myelosuppression to varying degrees is one of the more common toxicities and there is a risk of long-term bone marrow toxicity due to radiation. Identification of patients that are predicted to have short- and long-term toxicities from TRT is of major clinical interest, particularly as TRT moves to earlier disease states. Clonal Hematopoiesis (CH) has been detected in 25% of patients with solid tumors and is associated with a shorter overall and disease free survival**,** increased age, smoking, and prior radiation therapy, as well as increased risk of subsequent hematologic cancer in the future. Moreover, CH has also been seen in 36% of idiopathic cytopenias and such individuals have a 95% lifetime risk of MDS/AML. Exposure to radiation and chemotherapy increases penetration of CH and increases risk of MDS/AML. Patients with prostate cancer can have previous exposure to both chemotherapy and radiation and the CH clones may in turn be affected by TRT.

HYPOTHESES / OBJECTIVES: Our long-term goal is to identify CH signatures that predict short term and long-term bone marrow toxicities from TRT. Our *hypothesis* is that CH mutations have variable penetration based on specific PC therapies (especially TRT) and impact incidence of cytopenias and future risk of MDS/AML.

2. KEYWORDS

Prostate Cancer, Clonal Hematopoiesis , PSMA,

3. ACCOMPLISHMENTS

What were the major goals of the project?

AIMS / STUDY DESIGN

1. To determine the prevalence of pre and post treatment cytopenias in patients with and without clonal hematopoiesis (CH) at baseline. We will use a targeted deep sequencing based custom CH gene sequencing panel on samples from patients treated with PSMA-TRT.
2. To compare the longitudinal behavior of individual CH mutations, including the emergence or expansion of high-risk CH genes in response to TRT that are known to impact future risk of MDS. We will utilize serial samples in our cohort for this aim and use the high-risk gene mutations defined as presence of any one of the following genes: *DNMT3A, ASXL1, TET2, IDH, PPM1D, TP53*, spliceosome
3. To contrast the post treatment CH signatures in TRT patients with non-TRT treated patients. We will compare patients with similar prostate cancer characteristics treated with other therapeutic interventions.

Study Design: We have amassed a dataset from 11 prior completed and ongoing prospective clinical trials utilizing radiolabeled anti-PSMA targeted therapies. Many patients treated on historic studies have banked samples. The more recent trials included mandatory pre-treatment, 12-week, and progression samples, which have been banked. In addition, we have baseline and follow up samples

on non-TRT treated patients (hormonal therapy or chemotherapy) biobanked as well. We continue to enroll new patients and will continue to collect baseline and follow samples on both TRT and non-TRT patients. These patients are bio banked under out Universal Consent that allows research to be conducted on the specimens. While there are separate studies, collection of pre-treatment characteristics (including prior therapy, sites of disease, performance status, prognostic labs, etc) is standardized, as are some follow up time points and definitions of outcome variables. We have bloods collected at baseline and 3 months on everyone with additional blood draws on progression and long-term (>1 year) blood collection on patients in active follow up.

What was accomplished under these goals?

<u>Specific Aim 1</u>: To determine the prevalence of pre and post treatment cytopenias in patients with and without clonal hematopoiesis (CH
Major Task 1: Identification of prior patients with mCRPC treated with TRT
Subtask 1: Identification of patients treated on PSMA-TRT- (100% completion) We have completed all aspects of Subtask 1. During the course of the year, we obtained IRB approval for the study and also obtained HRPO approval. In addition we were able to track and collect peripheral blood buffy coat samples from patients treated with TRT who had samples already biobanked as part of ongoing bio banking research protocols. We have identified 98 patients treated with TRT who meet criteria for inclusion. We also collected the clinical data on cytopenias at baseline and follow up after TRT and created a Redcap database.
Subtask 2: DNA sequencing analysis (50% completion) We successfully extracted DNA from buffy coat specimens from baseline before starting TRT on these participants and are in the process of creating libraries for targeted next generation sequencing.
Major Task 2: Characterize prospective patients with mCRPC treated with TRT
Subtask 1: Collect data and samples from prospectively TRT treated patients (50% completion) We obtained IRB and HRPO approval for this subtask. We are prospectively collecting specimens and bio banking the peripheral blood at EIPM core
Subtask 2: DNA analysis (10% completion) DNA is being extracted on these specimens for future targeted next-generation sequencing

<u>Specific Aim 2</u>: To compare the longitudinal behavior of individual CH mutations, including the emergence or expansion of high-risk CH genes in response to TRT that are known to impact future risk of MDS.
Major Task 1:
Subtask 1: Complete clinical database in retrospective cohort (40% completion) We obtained IRB and HRPO approval. We have completed obtaining common clinical data from the retrospective cohort and completed clinical follow up for overall survival for these patients. We have already started the sequencing on patients who are deceased. These patients have completed follow up so we decided to perform sequencing on these patients first. We have a total of 230 samples for 98 patients that include baseline and follow up samples. In patients who are still alive, we are continuing to collect peripheral blood for long term research blood work.
Subtask 2: Complete clinical database in prospective cohorts (10% completion) This is in progress

<u>Specific Aim 3</u>: To contrast the post treatment CH signatures in TRT patients with non-TRT treated patients
Major Task 1: Identification of patients treated with non-TRT modalities
Subtask 1: Identification of patients treated with non-TRT treatments (20% completion) We obtained IRB and HRPO approval. We are identifying patients with similar PC characteristics and demographics that have blood already bio banked and collect DNA specimens. These include patients with chemotherapy treatment and hormonal treatment for castrate resistant prostate cancer.
Subtask 2: Identification of prospective controls simultaneously as the TRT trials are accruing to collect more samples from patients (Aim1) (15% completion) We are continuing to collect new patients treated with both TRT and non TRT therapies and biobanking both baseline and follow up samples.
Major Task 2: Comparison of pre and post CH signatures between TRT and non-TRT treated patients
Subtask 1: DNA sequencing analysis (10% completion) We obtained HRPO Approval

4. **IMPACT : Nothing to report**

5. **CHANGES/PROBLEMS**

Changes in approach and reasons for change

Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them

Nothing to report

Changes that had a significant impact on expenditures

There is an ongoing workforce shortage in regulatory department at our institution This has resulted in some delays in study start up and getting IRB approvals. This has not resulted in any significant impact on expenditures to date, and we were able to catch up. We are actively monitoring the study timelines.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents:
Significant changes in use or care of human subjects

Nothing to report

Significant changes in use or care of vertebrate animals

N/A

Significant changes in use of biohazards and/or select agents

N/A

6. **PRODUCTS**

- **Publications, conference papers, and presentations**

  Journal publications.

  Nothing to report

  Books or other non-periodical, one-time publications.

Nothing to report

Other publications, conference papers and presentations.

Nothing to report (but will have abstract presentation/publication(s) to report in the next reporting period.

- **Website(s) or other Internet site(s)**

  Nothing to report

- **Technologies or techniques**

  Nothing to report

- **Inventions, patent applications, and/or licenses**

  Nothing to report

- **Other Products**

Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Personnel	Role	Person Month	Percent Effort
Pinkal Desai MD MPH	Principal Investigator	1.8	15%
Scott Tagawa, M.D.	Co-Investigator	1.2	10%
Andrea Sboner M.D.	Co-Investigator	0.6	5%
Neil Bander, MD	Collaborator		0%
Karla Ballman Ph.D	Co-Investigator	0.4	3%
Monica Guzman	Co-Investigator	0.2	2%
Laura Tarnbay	Research Program	0.2	2%

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Karla Ballman has left the institution recently and is being replaced on the grant with Oleksandr Savenkov.

What other organizations were involved as partners?

N/A

8. SPECIAL REPORTING REQUIREMENTS N/A

9. APPENDICES : N/A