Using PSA Dynamics to Optimize Docetaxel Scheduling in Metastatic Prostate Cancer

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PROSTATE CANCER

1 in 9 American men will get prostate cancer during his lifetime.
Androgen deprivation therapy has been the mainstay treatment for over 70 years!
Median survival in metastatic prostate cancer patients receiving ADT is ~3 years.
TREATING PROSTATE CANCER

Is it more beneficial to give chemotherapy prior to the development of castration resistant disease?
Early chemotherapy extended overall survival by 13 months in castration sensitive metastatic patients when compared to ADT alone.
What is the optimal time to administer chemotherapy? Is it patient-dependent?

Administering chemotherapy after castration resistant PCa development extended overall survival by just 2.4 months.
BIOMARKER

Castration Resistant

- 38 patients
- ADT alone followed by up to 10 cycles of chemotherapy

Castration Naïve

- 56 patients
- ADT with up to 6 cycles of chemotherapy concurrently
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## MATHEMATICAL MODEL

<table>
<thead>
<tr>
<th>Basal</th>
<th>Secretory</th>
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### Intact Prostate (normal androgen)

- Stem
- Transit Amplifying
- Differentiated

### Castrate Prostate (decreased androgen)

- Stem
- Transit Amplifying
- Differentiated

- **Longevity**
- **Differentiation**
- **Self-Renewal**
- **Invasion**

*restore androgen*

Isaacs & Coffey, The Prostate, 1989
MATHEMATICAL MODEL

PCa stem cells

Differentiated cells

Prostate-specific antigen

\( \lambda \)

\( \rho \)

\( \varphi \)

\( p_s \)

\( \delta_s \)

\( \delta_D \)

\( \alpha \)

\( \alpha \)

Chemotherapy

ADT
MATHEMATICAL MODEL

\[
\frac{dS}{dt} = \left(\frac{S}{S + D}\right) p_s \lambda S - \delta_p T_{xD} S
\]

PCa stem cells

Differentiated cells

Prostate-specific antigen

\( \lambda \)

\( \alpha \)

\( \rho \)

\( \delta_p \)

\( \delta_S \)

\( p'_s \)

Chemo

\( \phi \)

\( dS \)

\( dS/dt \)

\( S \)

\( S + D \)

\( T_{xD} \)

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CATMO 2020
MATHEMATICAL MODEL

\[ \frac{dS}{dt} = \left( \frac{S}{S + D} \right) p_s \lambda S - \delta_S T_{xD} S \]

\[ \frac{dD}{dt} = \left( 1 - \left( \frac{S}{S + D} \right) p_s \right) \lambda S - \alpha T_x D - \delta_D T_{xD} D \]
MATHEMATICAL MODEL

\[
\begin{align*}
\frac{dS}{dt} &= \left(\frac{S}{S+D}\right) p_S \lambda S - \delta_S T x_D S \\
\frac{dD}{dt} &= \left(1 - \left(\frac{S}{S+D}\right) p_S\right) \lambda S - \alpha T x D - \delta_D T x_D D \\
\frac{dP}{dt} &= \rho D - \varphi P
\end{align*}
\]
MODEL CALIBRATION

Castration Resistant

Patient 105

Eight cycles of chemotherapy with ADT

ADT alone

Stem cells die in response to chemo

Castration Naïve

Patient 109

Six cycles of chemotherapy with ADT

ADT alone

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EARLY VS. LATE

Castration Resistant

Patient 148

Early > Late
EARLY VS. LATE

Castration Naïve

Early > Late
EARLY VS. LATE

Patient 121

Patient 104

Early < Late
TAKEAWAYS

• Optimal chemotherapy timing is patient-specific

• Stem cell self-renewal was primary driver of resistance in intermittent hormone therapy study
  • Does this separate patients who need chemo early vs late?
CAN WE LEARN THIS EARLY?

Learn patient-specific parameters and simulate chemo?
SUMMARY

• Extended stem cell model to investigate optimal time to administer chemotherapy after hormone therapy

• Model can accurately describe PSA dynamics in both early and late chemotherapy settings

• Model simulations imply that timing may be patient-specific, but may be best to give prior to mCRPC development