Intermittent (IAD) versus continuous androgen deprivation (CAD) in hormone sensitive metastatic prostate cancer (HSM1PC) patients (pts): Results of SWOG 9346 (INT-0162), an international phase III trial

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Background

- Continuous androgen deprivation is the standard of care for patients with metastatic hormone sensitive prostate cancer.
- Despite high initial response rates, hormone resistance occurs in the vast majority of hormone sensitive metastatic prostate cancer patients treated with androgen deprivation. The median survival for patients treated with CAD is 2.5-3 years.
- Hormone resistance is an adaptive process with activation of genes resulting in the production of autocrine/paracrine growth factors that contribute to maintaining the viability of prostate cancer cells in spite of androgen deprivation.
- Replacing androgens before castration resistance is hypothesized to maintain prostate cancer androgen-dependence and sensitivity.
- Pre-clinical data in androgen-dependent tumor models showed that progression of prostate cancer was associated with a 500x increase in the proportion of androgen-independent stem cells
- Apoptosis of stem cells could be re-induced with IAD, and IAD prolonged the mean time to androgen resistance.
- Early clinical trial data showed IAD was feasible and improved quality of life.
- The primary objective of this study was to determine if IAD was non-inferior to CAD in terms of overall survival (OS) in patients with metastatic hormone-sensitive prostate cancer.

Methods

- Patients with hormone sensitive metastatic prostate cancer with performance status 0-2 and PSA ? 5 ng/ml were treated with 7 months of goserelin and bicalutamide.
- Patients achieving PSA ?4 ng/ml at month 6 and 7 were stratified by prior receipt of neoadjuvant androgen deprivation or finasteride, performance status, and disease extent (minimal, extensive). They were then randomized to CAD or IAD.
- Men on IAD had monthly PSAs monitored while not on androgen deprivation. Therapy was resumed when the PSA increased to 20 ng/ml for baseline values ? 20 ng/m or a return to baseline for PSA < 20 ng/ml. If after 7 months of induction, normalization criteria were met, another observation period was started. Otherwise, patients received CAD.
- Primary objective: To assess if OS with IAD is non-inferior to CAD using a one-sided test with an upper bound hazard ratio=1.20, adjusting for stratification factors.
- Sample size: 756 patients per arm, with type I and II error rates of 0.05 and 0.10.
- Secondary endpoints: quality of life (impotence, libido, energy) and physical emotional function. Secondary end points were not reported in this presentation.
- The sample size and upper bound of the hazard ratio was determined assuming a post-randomization median survival for CAD of 3 years.
- The study was activated in May 1995 and closed in September 1998.

Results

- 3,040 pts were accrued by SWOG, CALGB, ECOG, NCIC, and EORTC.
- After 7 months of CAD, 1,535 eligible patients achieved PSA ? 4.0, and were randomized to CAD (759 pts) or IAD (770 pts).
- The two treatment groups were well-balanced across prognostic criteria such as PSA, performance status, disease extent, age, bone pain, prior androgen deprivation therapy, and Gleason score.
- Median follow-up was 9.2 yrs.
- Median survival for all patients from study entry was 3.6 years, and 10 year OS was 17%.
- For CAD patients, median survival from time of randomization was 5.8 years and 10 year OS was 29%.
- For IAD patients, median survival from time of randomization was 5.1 years and 10 year OS was 23%. Hazard ratio for IAD/CAD was 1.09, 95% CI 0.95, 1.24.
- IAD was not non-inferior for any subset of patients except for those with extensive disease, HR 0.96, 95% CI0.79, 1.16 (p=0.64.)
- Prostate cancer was cause of death in 56% of CAD and 64% IAD patients.
- Grade 3/4 related adverse events such as cardiac events, flu-like symptoms, gastrointestinal toxicity, etc.: IAD 30.3%, CAD 32.6%.

Author's conclusions

- In hormone sensitive metastatic prostate cancer, IAD is not proven to be non-inferior to CAD.
- For extensive disease patients, IAD was non-inferior; however, IAD was statistically inferior in minimal disease patients suggesting that CAD is the preferred treatment in this group.
- In this international, cooperative group phase III trial in patients with metastatic hormone sensitive prostate cancer, IAD was inferior to CAD based on a pre-specified definition of survival comparability.
- CAD continues to be the standard of care.

Clinical Implications

- The discovery of androgen-dependence of prostate cancer cells was made in the 1940s. Androgen receptors are highly expressed on prostate cancer cells and androgens directly stimulate prostate cancer cells to survive.
- Although > 90% of patients initially respond to androgen deprivation therapy, there are compelling theoretical reasons to consider IAD, including:
- - Prolonged time to hormone resistance
  - Minimization of adverse events from androgen deprivation (hot flashes, weight gain, bone fracture, etc.)
  - Improvement in quality of life
- Numerous phase II trials suggest that IAD has comparable efficacy, reduced toxicity, and improved quality of life compared to CAD; however systematic review of these studies demonstrates wide variability in treatment regimens, stage of prostate cancer, and starting/stopping rules.
- There are seven recently reported phase III trials comparing IAD to CAD in both metastatic and non-metastatic prostate cancer. While most studies showed no difference in survival between IAD and CAD, the cohorts were not powered to evaluate survival and progression end points were difficult to measure.
- The SWOG/Intergroup study represents a tremendous effort to capture data for over 3,000 patients over the 17 years since the study has been activated. The study is also a testament to the power of cooperative groups in pooling large numbers of patients to answer a study question.
- Weakness of the study include:
- - Survival was much better than expected for the control arm, and therefore the upper limit of the hazard ratio chosen (1.20) may not have been an appropriate cut-off point.
  - The definitions for minimal and extensive disease were non-standard definitions, confounding the subgroup analysis, which found a lack of inferiority for IAD in patients with extensive disease. Furthermore, this subgroup

analysis must be interpreted with caution as the analysis was not planned, and the study was not powered to address overall survival in subgroups.
    - Although improved quality of life is stated as a potential benefit of IAD, patients on the IAD arm of this study spent 2/3 of the study time on androgen deprivation therapy. Given that testosterone reconstitution can take up to 4 months, adequate recovery time may not have been granted for improvements in quality of life.
- Of note, none of the existing randomized trials on IAD have shown a superior cancer outcome with IAD, and therefore CAD should remain the standard of care for all patients.
- Further study is warranted given that prostate cancer continues to be the second leading cause of cancer death in men. Instead of IAD, potential for therapeutic gain may rest with novel drugs targeting androgen signal pathways, such as abiraterone, or inhibition of androgen receptor signaling.
