1.0 Abstract

Title

Canadian Real-Life Evaluation of the Effectiveness of Lupron in the Management of Prostate Cancer (CRONOS)

Keywords

Lupron, leuprolide acetate, real-life, effectiveness, safety, prostate cancer

Rationale and Background

Prostate cancer (PCa) is the most common malignancy in men and the second leading cause of cancer-related male deaths in the western world (1). An overall upward trend in the incidence rate of PCa has been observed in the last two decades, which is likely due to increased early detection, increased life expectancy and possible changes in risk factors. Furthermore, there has been a subtle but clear decrease in mortality (1,2) in large part due to prostate specific antigen (PSA)-based screening and aggressive local, but not systemic, treatment (3).

The management of early PCa is controversial and treatment decision making is often based on patient and provider preferences taking into account the risks and benefits of therapies and disease progression. At the time the study was developed, there were no definitive guidelines for the treatment of PCa and, in many cases, the decision regarding surgical versus non-surgical treatment depended on the individual patient or physician. Similarly, the decision whether or not, and when to use hormone treatment may vary between physicians and individual patients. As androgen deprivation therapy (ADT), the principal indication for Lupron® (leuprolide acetate, LA) is the management of advanced or refractory (CRPC; castration resistant prostate cancer) PCa and is applied either before surgery and radiation as neoadjuvant or after surgery and radiation as adjuvant treatment (4).

It was anticipated that there would be significant variation with respect to the management of PCa and the integration of LA treatment that could be affected by regional access to care, the experience and background of the treating physician, the province and rural versus urban location, university versus community treatment site. This variation with respect to the management of PCa would imply that certain patients may be receiving suboptimal care. While the efficacy and tolerability of LA in the management of advanced PCa has been demonstrated in several controlled clinical trials (4-11), the question whether these results can be extrapolated to effectiveness in the real-life setting, particularly in Canada, remains unanswered. Furthermore, since PCa presents a significant burden of illness through the physical and emotional manifestations that significantly affect the patient's quality of life as well as loss of productivity and direct and indirect health care costs, assessment of the impact of different approaches to the management of PCa on these patient centric outcomes was of paramount importance. Given that patient reported outcomes have a cultural and regional influence, the assessment of these outcomes in specific regions was also of high relevance and importance in the assessments of regional and global benefit–risk ratios.

The aim of the current observational study was to conduct an evaluation of the effectiveness of LA in the management of PCa under Canadian routine care. The variation and its determinants with respect to management practices of this patient population were also to be assessed.

Research Question and Objectives

The primary objective of the current study was to describe the real-life effectiveness of LA in the management of advanced PCa in Canada.

The secondary objectives were:

1. To describe the variation in patient profile and the management approach (adjuvant, neo-adjuvant, intermittent, continuous) utilized in the treatment of advanced PCa with LA in Canada.

2. To compare the real-life effectiveness, impact on quality of life and sexual function of LA as neo–adjuvant versus adjuvant therapy and intermittent versus continuous use in the management of patients with advanced PCa in Canada.

3. To conduct a health economic evaluation of LA in the management of advanced PCa within the Canadian health care system.

4. To assess the tolerability of LA in the management of advanced PCa under real-life conditions in Canada.

Study Design

This was a Canadian post-marketing observational study (PMOS) utilizing a prospective cohort design. Patients with PCa who had been prescribed LA were included in the study cohort and were followed for a maximum of 36 months with recommended follow-up assessments at 3 months, 6 months and every 6 months thereafter. Given the observational nature of the study all treatment decisions and the actual follow-up schedule were as per the routine practice at each participating site and the judgment of the treating physician.

Setting

There were 37 physicians who recruited patients across Canada between 07-Jun-2011 and 22-Jul-2013. Patients were followed for a maximum of 36 months.

Subjects and Study Size

In order to detect a PFS rate of 77% with a precision tolerance of ±7%, 90% power and 5% significance, and assuming 25% drop out rate, a total of 550 patients were required for this study. For additional details on the study size refer to Section 9.6.

A total of 552 patients were enrolled and included in the intent-to-treat (ITT) population of whom 259 (46.9%) completed the full study and 293 (53.1%) discontinued prematurely. The main reasons reported for discontinuation were loss to follow-up, 'other', death, and withdrawal of consent in 51 (9.2%), 51 (9.2%), 47 (8.5%) and 44 (8.0%) patients, respectively. On average, during the study, patients were exposed to LA for 22.2 (SD: 13.2) months.

Variables and Data Sources

The primary outcome measure of the current study was the progression-free survival (PFS), defined as the time from patient recruitment to biochemical progression based on doubling of prostate-specific antigen (PSA) velocity or PSA >5.0 ng/mL, objective tumor progression (RECIST criteria) or death. Given changes in the definition of biochemical progression since the time the study was developed, a second definition was used for PFS, specifically the time from patient recruitment to change to an absolute value of PSA>2 ng/mL on at least 2 consecutive testings, objective tumor progression (RECIST criteria) or death.

Secondary outcome variables included changes in the following parameters between baseline and each follow-up visit, including the final assessment at month 36: incidence of CRPC defined as PSA > 2 ng/mL on at least 2 consecutive tests; testosterone; PSA; patient quality of life (QoL) assessed with the validated self-administered Functional Assessment of Cancer Therapy (FACT-G and FACT-P) questionnaires; sexual function assessed with the validated International Index of Erectile Function (IIEF-5)

questionnaire; health care utilization and out of pocket expenses; spontaneously reported SAEs and other AEs, including AEs leading to study discontinuation and unusual failure in efficacy; compliance with treatment; changes in medical history; and concomitant medications for PCa.

Results

At 36 months, the cumulative probability for PFS was between 18.9% and 29.4%, depending on which definition of biochemical progression concerning PSA levels was used (primary vs. alternative, respectively). The estimated mean PFS ranged between 20.8 (95% CI: 18.0 – 23.4; primary definition) months and 21.9 (95% CI: 26.9 – 32.0; alternative definition) months; or between 19.1 and 30.5 months based on the median PFS for each definition. Higher age and use of any concomitant PCa treatment were identified as significant predictors of poor outcome. Province of residence was also found to have an impact on PFS suggesting differences in patient management and physician practices across provinces.

A statistically significant reduction in testosterone to castrate or sub-castrate levels was observed in most patients as early as 3 months, which were maintained for a mean (SE) of 31 (0.7) months (lower-bound level of the confidence interval for the median: 38 months). Similarly, significant reductions in PSA levels were observed with an estimated mean (SE) time to CRPC of 26 (0.4) months.

In terms of sexual function and health-related QoL, despite statistical reductions (mean changes below the threshold of clinical significance, i.e. 4 points) in the IIEF-5 score during the study, FACT-G and FACT-P remained relatively stable with absolute changes below the thresholds for clinical relevance.

Subgroup analyses that assessed variations in the patient profile based on LA management approach (adjuvant vs. neo-adjuvant), type of treatment (continuous vs.

intermittent), and clinic setting (university vs. community), showed significant differences in patient management. This was particularly true in the subgroup analysis by type of LA treatment, where patients treated with continuous therapy were less likely to have been previously treated with LA or ADT in general, and had higher Gleason scores. Furthermore, patients treated with continuous LA therapy were more likely to reside in Quebec and less likely in British Columbia as compared to patients using intermittent LA therapy.

Discussion

Overall, the results of the current study suggest that real-life effectiveness of LA is comparable with the efficacy previously reported in controlled clinical trials (see Section '*11.1 Key Results*'). General and PCa-specific health-related QoL remained below the thresholds for clinical relevance, which corroborates good treatment tolerance and is in line with treatment targets in contemporary routine clinical practice.

Considerable differences in the profile of patients treated with continuous vs. intermittent LA therapy and patients seen in university vs. community clinics which indicates significant variation in patient management based on patient profile but also regional particularities and individual physician preferences. This small area variation is an important finding.