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Clinical Trial Results

Temsirolimus Maintenance Therapy After Docetaxel Induction in Castration-Resistant Prostate Cancer

URBAN EMMENEGGER,[a,b] CHRISTOPHER M. BOOTH,[c] SCOTT BERRY,[a] SRIKALA S. SRIDHAR,[d] ERIC WINQUIST,[e] NESAN BANDALI,[a] ANNABELLE CHOW,[b] CHRISTINA LEE,[b] PING XU,[b] SHAN MAN,[b] ROBERT S. KERBEL,[b] YOO-JOUNG KO[a]

[a]Odette Cancer Centre and [b]Sunnybrook Research Institute, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada; [c]Queen's University Cancer Research Institute, Kingston, Ontario, Canada; [d]Princess Margaret Cancer Centre, University of Toronto, Toronto, Ontario, Canada; [e]London Health Sciences Centre, London, Ontario, Canada

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AUTHOR SUMMARY

LESSONS LEARNED

Temsirolimus maintenance therapy after docetaxel induction chemotherapy

- is safe in patients with castration-resistant prostate cancer, although biochemical or tumor responses are rare;
- does not diminish quality of life; and
- delays radiological and/or symptomatic progression by approximately 6 months.

ABSTRACT

Background. No standard therapy is available for men with castration-resistant prostate cancer (CRPC) who have responded to docetaxel and do not yet have disease progression. Hence, we designed a single-arm phase II trial to explore whether the mTOR inhibitor temsirolimus can maintain the response to docetaxel without compromising quality of life.

Methods. After successful docetaxel induction (75 mg/m^2 every 3 weeks; 6–10 cycles), 21 CRPC patients underwent temsirolimus maintenance treatment (25 mg weekly; 4 weeks per cycle). The primary endpoint was the time to treatment failure (TTTF) (i.e., radiological and/or symptomatic progression). The secondary endpoints included the tumor response rate (RECIST 1.0), safety (National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0), quality of life (Functional Assessment of Cancer Therapy-Prostate [FACT-P]), pain (Present Pain Intensity [PPI] scale), prostate-specific antigen (PSA) parameters, including time to PSA progression (TTPP) according to Prostate Cancer Clinical Trials Working Group criteria, and serial enumeration of circulating endothelial cells (CECs) and endothelial progenitor cells (CEPs).

Results. Patients received a median of 7 cycles of temsirolimus (range, 1–28), resulting in a median TTTF of 24.3 weeks (95% confidence interval [CI], 16.1–33.0), 1 partial tumor response (4.8%), 1 PSA response (4.8%), and a median TTPP of 12.2 weeks (95% CI, 7.8–23.9). Grade 3-4 adverse events were infrequent, and FACT-P and PPI scores remained stable during treatment. CECs did not predict clinical benefit, and CEPs were not consistently detectable.

Conclusion. Temsirolimus maintenance therapy after successful docetaxel induction is feasible, does not adversely affect quality of life, and, in this exploratory single-arm phase II study, resulted in a median TTTF of 24.3 weeks. ***The Oncologist*** 2015; 20:1351–1352

DISCUSSION

In the absence of progression or prohibitive toxicity, docetaxel chemotherapy is usually administered for up to 10 cycles for the treatment of CRCP. However, the optimal duration of docetaxel therapy has not been determined. As opposed to treating to progression or to a finite number of cycles, two different strategies have been explored in preliminary studies: (a) intermittent docetaxel chemotherapy (supplemental online Table 1 [available online]); and (b) maintenance therapy using various agents (supplemental online Table 2 [available online]). We present the findings of the first study of temsirolimus maintenance therapy in 21 CRPC patients after successful docetaxel induction. The

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Correspondence: Urban Emmenegger, M.D., Odette Cancer Centre, Sunnybrook Health Sciences Centre, University of Toronto, 2075 Bayview Avenue, Toronto, Ontario, Canada. Telephone: 416-480-4928; E-Mail: urban.emmenegger@sunnybrook.ca Received May 25, 2015; accepted for publication September 11, 2015; published Online First on November 5, 2015. http://dx.doi.org/10.1634/theoncologist.2015-0220

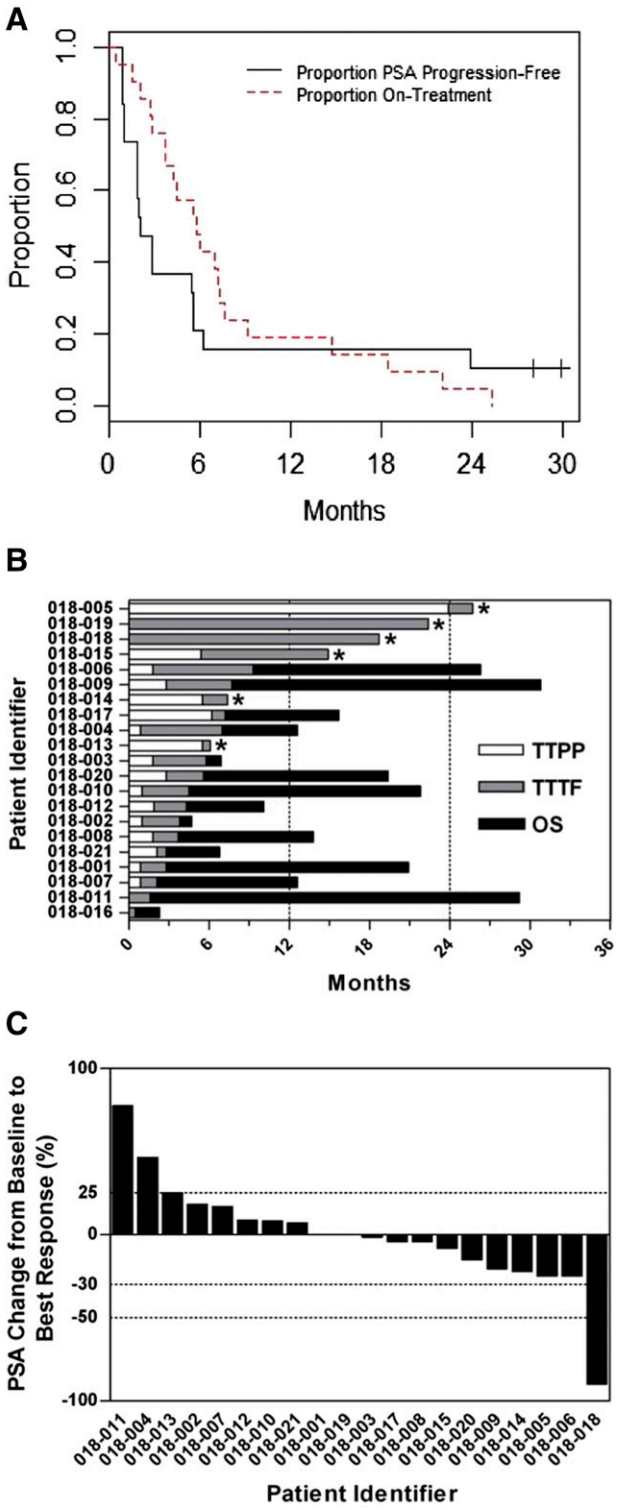

Figure 1. Treatment outcomes. **(A):** The median TTTF (i.e., radiological and/or symptomatic progression) was 24.3 weeks (95% CI, 16.1–33.0). The TTPP was 12.2 weeks (95% CI, 7.8–23.9). **(B):** Depiction of TTPP (white bars), TTTF (gray bars), and OS (black bars) in individual patients ranked according to TTTF. Asterisks indicate patients alive at study termination. **(C)**: Waterfall plot of percentage of PSA changes from baseline to best response of 20 evaluable patients, revealing a PSA response >50% in 1 patient and any PSA decline in 10 patients.

Abbreviations: OS, overall survival; PSA, prostate-specific antigen; TTPP, time to PSA progression; TTTF, time to treatment failure.

rapalog mTOR inhibitor (mTORi) temsirolimus was chosen because of the high rate of PI3K-AKT-mTOR pathway abnormalities in CRPC, preclinical temsirolimus activity in various prostate cancer models, and the favorable safety profile of rapalog mTORis.

Temsirolimus maintenance therapy resulted in a median TTTF of 24.3 weeks (95% CI, 16.1–33.0) (Fig. 1A; Table 2 [available online]). Biochemical progression preceded symptomatic (61.9%) and/or radiological (23.8%) progression in most patients, accounting for a TTPP of 12.2 weeks (95% CI, 7.8–23.9) (Fig. 1A, 1B; Table 2 [available online]). Aside from a single PSA and a partial tumor response, we documented any PSA decline in 10 of 20 evaluable patients, and stable disease was observed in 61.9% of patients (Fig. 1C; Table 2 [available online]). Grade 3 treatment-related side effects such as hyperglycemia were infrequent (9.5%), and one grade 4 thromboembolic event occurred. One patient withdrew consent because of grade 2 peripheral edema, considered "possibly" treatment related. Temsirolimus did not diminish quality of life as assessed using the FACT-P questionnaire (Fig. 2A), nor did we observe significant changes in pain (Fig. 2B) or performance status (data not shown) during treatment.

Our findings confirm the typically cytostatic effects of rapalog mTORis observed in different stages of CRPC (supplemental online Table 3 [available online]), possibly due to only partial PI3K-AKT-mTOR pathway inhibition and compensatory activation of other signaling pathways. However, considering the acceptable safety profile of temsirolimus, the TTTF of 24.3 weeks compares favorably with treatment-free intervals of approximately 4–5 months observed in intermittent chemotherapy trials (supplemental online Table 1 [available online]). Furthermore, maintenance temsirolimus is superior to ketoconazole or sunitinib, while similar results were achieved with granulocyte macrophage colony-stimulating factor (supplemental online Table 2 [available online]).

Despite significant changes in the CRPC treatment landscape since the inception of this study in 2008, postdocetaxel maintenance strategies remain relevant. The PI3K-AKT-mTOR pathway contributes to resistance to novel androgen receptor pathway inhibitors such as abiraterone and enzalutamide. However, given the pharmacological shortcomings of rapalog mTORis, future trials might study ATP site mTORis or dual PI3K/mTORis, or select patients with genetic features predicting sustained responses to mTORis.

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