The effects of using the RxTimerCap© on patient medication adherence.

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ABSTRACT

Specific Aims: Medication adherence tools and technologies can have a significant impact on the level of drug therapy continuation as well as improved outcomes. The RxTimerCap© is a device that aims to act as a medication adherence cap with an embedded timer to indicate the time since the medication was last taken. Our aim was to assess if this cap technology would aid in increased drug adherence and duration of therapy with abiraterone (Zytiga®).

Methods: The study was a prospective, single-center, interventional study that included males 18 or older being treated with Zytiga for castration-resistant metastatic prostate cancer. Medication possession ratio (MPR) and duration on therapy were the primary measures used to assess if there would be improved adherence. Paired t-tests were used to analyze the data and assess the significance of the outcomes.

Main Results: There was no significant difference between patients in MPR ($p = 0.50$) or in the duration of treatment ($p = 0.20$).

Conclusions: The difference in adherence rates for patients using the RxTimerCap© and those using the standard vial cap were non-significant. The limited size of our study population and short study duration may have led to these undifferentiated outcomes. Future studies should examine this type of adherence technology in a larger sample of patients with a prolonged window of observation to better assess the benefits of using the RxTimerCap©.

INTRODUCTION

There are diseases that require strict medication therapy adherence in order to achieve disease control or resolution. A report published by the World Health Organization (WHO) in 2003 indicated that effective and innovative strategies for improving medication adherence can more significantly influence human health compared with advancements in medical techniques.[2] Patients often experience delays and forgetfulness in the consumption of their prescribed medications.[2] As such, companies have produced products such as RxTimerCaps© as a technological way to improve adherence.

Prostate cancer is a disease in which adherence-improving technology can potentially make a substantial positive impact. The pharmacotherapy for prostate cancer requires strict adherence and deviating from the prescribed drug schedule often leads to disease complications. Less than 50% of patients with a new diagnosis of castrate-resistant prostate cancer survive more than 3 years. Zytiga (abiraterone acetate) is converted in vivo to abiraterone, an androgen biosynthesis inhibitor, to inhibit 17α hydroxylase/C17, 20-layse (CYP 17), and block androgen biosynthesis (precursor to testosterone). It is effective in castrate-resistant prostate cancer because it targets the enzyme that is expressed in testicular, adrenal, and prostate tumor tissues that androgen deprivation therapies do not reach.[5] Prednisone co-administered with Zytiga compensates for the reduction in cortisol and blocks the increase of adrenocorticotropic hormone. Zytiga trial results for median overall survival vs. placebo and goal of therapy is to take until progression, showing established efficacy, safety and tolerability in metastatic castrate resistant prostate cancer.

In order to obtain the most benefit from Zytiga drug therapy, it is essential that patients regularly take this oral medication as prescribed with a goal of a high adherence rate. The purpose of a digital timer on a pill vial such as RxTimerCaps© is to help facilitate this goal. However, there have

been no studies on the RxTimerCaps© and its effect on adherence rates. The purpose of this study is to evaluate the effects of RxTimerCaps© on adherence in patients taking Zytiga.

METHODS

Patients in each group were different and were randomly selected from a list of numerically ordered patients to either receive an RxTimerCaps© or be included in the control group. Study dates were from October 11, 2016 to March 1, 2017. Patients were assigned random patient numbers by Avella. Those numbers were then randomly assigned to either the intervention or control group. For the intervention group, Avella filled the prescription equipped with a RxTimerCap©. For the control group, the patients received their medication in regular vials with a standard cap. A total of 26 patients were included in this study, 7 patients in the interventional arm and 19 in the control arm. The RxTimerCap© is a product that addresses the issue of adherence and allows the patient to see when the cap was last removed from the bottle. Patients were counseled on device use upon receiving the RxTimerCap© at the pharmacy in order to walk them through how to use it, which 2 patients in the intervention group declined.

Data was collected from the electronic records within the Avella computer system. To store data on the excel file, columns were created, so the data was orderly and easily retrievable. Pertinent data was collected and manually entered in a secured and encrypted excel sheet with most of the information necessary for this study already collected in the database and requiring no change. Parameters measured in the databases were the initial fill date, last fill date, total day supply dispensed, last prescription day supply, total number of fills, Mean Possession Ratio (MPR), the length of therapy (days), age (years). Surveys were sent to patients in the intervention group after the study to evaluate their opinions regarding their use of the RxTimerCap©.

MPR was calculated for all the study participants and standard deviations for the control and intervention group were calculated as well. A t-test was used to compare the means of the independent groups for looking at MPR. A Mann-Whitney U Test was used to compare medians between the two groups for duration on therapy.

Design

The study was a prospective, single-center, interventional study. The control group and the intervention group were the prospective groups. This study was approved by the University of Arizona Institutional Review Board (IRB) program responsible for human subjects research.

Subjects

Patients included in the study were males ≥18 years old and actively filling Zytiga prescriptions at Avella Specialty Pharmacy in Las Vegas, Nevada. Individuals were excluded if they did not fill their Zytiga prescriptions at the single-center location associated with Avella.

Intervention

RxTimerCaps© were used as the intervention tool that indicated the amount of time elapsed since the last time the bottle was opened. Each patient included in the intervention arm was provided with an opportunity for a counseling session completed with a pharmacist. An Avella staff member explained the purpose of the cap with each consenting patient and explained how the cap would work.

Measures

A data dictionary was used to compile important information about the study subjects and track important data points. Duration of treatment was determined by looking at the reported first medication fill date through the most recent or active fill date. The MPR was assessed by comparing the sum of days supply in the study period to the number of days in the period

$$MPR = \frac{Total\ Rx\ Supply\ (days)}{last\ Rx\ date - first\ Rx\ date\ +\ last\ Rx\ day\ supply}$$

This information was saved and analyzed using a protected excel sheet with columns indicating the data type and Avella-generated identification numbers acting to distinguish unique patients.

Data Collection

The collection of data was undertaken by staff at Avella pharmacy who accessed patient medication fill history and demographic information in order to obtain the necessary information.

Data analysis

T-test analysis was used to examine differences in MPR between the control and intervention groups in order to infer levels of adherence based on study treatment. A Mann-Whitney U test was used to assess differences in duration on therapy between the control group and the RxTimerCaps© group. The medians were calculated for each group and were compared to one another.

RESULTS

The main demographics measured for the study are shown in table 1. Both treatment groups had similar characteristics for both demographic variables. The outcomes of the statistical comparisons between the two treatments regarding MPR are shown in table 2. Based on the data and statistical analyses conducted, there were no significant differences between groups in increased adherence based on treatment received ($p = 0.50$). This result can be seen under the values for the MPR (medication possession ratio) in the table. In comparing the difference between the treatment arms when it came to duration of therapy by looking at the median days, we also found no significant difference in treatment choice ($p = 0.20$). Of those patients in the control arm that stopped using the medication, there were numerous causes for discontinuation (table 3).

4 out of the 7 intervention patients returned surveys about their experience using the RxTimerCap©. Patients showed positive experiences overall with a few exceptions. One of the

4 patients mentioned that they experienced problems using the cap. All the returned surveys indicated that they would recommend the cap to a friend needing help with medication adherence (table 4).

DISCUSSION

In comparing the intervention group to the control, we did not find any significant differences in the MPR or duration on therapy, which were our de facto measures of adherence in the study population. These outcomes are not completely unexpected as adherence is a concern that is managed over a period of not just months, but years as well. Our study period encompassed a length of time that may not have been sufficient to bear out differences in missed doses, forgetfulness, or inabilities to access medications due to numerous barriers such as cost, transportation, or drug availability. There have been extensive studies conducted on adherence mechanisms and tools to help increase the rate of dose continuity and associated benefits. In a randomized controlled trial by Vervloet et al., SMS reminders were used to remind and alert diabetic patients to refill their medications based on pharmacy fill information. Patients were divided into three groups with both short- and long-term SMS reminder intervention groups compared to a control group. After 1 year, mean refill adherence of participants in the SMS group was significantly higher than that of those in the control group, with a mean difference of 15%. After 2 years, participants who received refill reminders had a stable adherence rate of 80.4%, and those who did not approached their baseline level of 65.5% adherence. This not only displays the importance that adherence reminders play in increased adherence, but the need to assess these changes over a longer period of time.

In a 12-month randomized controlled trial conducted by Vollmer et. al., patient were assigned to receive automated voice reminders, personalized letters, live phone calls, or were included in the control group. The study assessed the difference in adherence rates not to all drugs prescribed, but specifically ACE/ARBs and statins. In both the voice reminder and voice reminder + phone call groups, statin adherence was significantly increased compared to the

control group. In both the voice reminder and voice reminder + phone call groups, ACEI/ARB adherence was also significantly increased compared to the control group. There also also a significant reduction in LDL-cholesterol levels in the voicemail + phone call group compared to the control group.

The sample size included in this study was insufficient to gauge the impact that a simple adherence tool would have on patient adherence. Future studies might consider including not only more patients, but different patient types as the type of patient receiving treatment for cancer with expensive medications may already be treatment-experienced and understands the need for utmost maintenance of therapy versus a patient on medications for prevention and treatment of chronic diseases.

Limitations that accompany this sort of medication adherence solution is inherent to the tool itself and applies to most technologies using a similar approach. This type of management approach can be difficult to adjust to for many patients including the elderly who make up the majority of these users. Additionally, there is the issue of cost for the cap that must be incurred by either the insurance payer, the patient, or the dispensing pharmacy. Implementation costs for many of these adherence tools in general considering the time spent by a pharmacist to educate and monitor the patient and developing these programs may outweigh the economic and health outcome benefits. This would decrease the extent to which these types of solutions could be used across a wide array of patient groups. Another limitation is that patients are proactively called for refills and adherence is checked through modified morbidity scale and adverse effect symptoms. This makes it difficult to realize the effects of the medication adherence device alone and why this specialty pharmacy may be higher than a retail pharmacy.

CONCLUSIONS

The adherence rates in patients using the RxTimerCap© and those using the standard vial cap were not different. Improved adherence may be seen with more patients randomly selected to receive a timer cap to make them aware of missed or late doses.

REFERENCES

1) Vervloet, M., Van Dijk, L., De Bakker, D., Souverein, P., Santen-Reestman, J., Van Vlijmen, B.,Bouvy, M. (2014). Short and Long-term effects of real-time medication monitoring with short message service (SMS) reminders for missed doses on the refill adherence of people with Type 2 diabetes: Evidence from a randomized controlled trial. *Diabetic Medicine, 31*(7), 821-828. doi:10.1111
2) Huang, H., Li, Y., Chou, Y., Hsieh, Y., Kuo, F., Tsai, W., . . . Chuang, C. (2013). Effects of and satisfaction with short message service reminders for patient medication adherence: A randomized controlled study. *BMC Medical Informatics and Decision Making, 13*(127).
3) Volmer, W. M., Owen-Smith, A. A., Tom, J. O., Laws, R., Ditmer, D. G., Smith, D. H., . . . Rand, C. S. (2014). Improving Adherence to Cardiovascular Disease Medications With Information Technology. *The American Journal of Managed Care*, 20, SP502-SP510. Retrieved January 20, 2016.
4) Cocosila, M., Archer, N., Haynes, R., Yuan, Y., (2008). Can wireless text messaging improve adherence to preventive activities? *Results of a randomized controlled trial. International Journal of Medical Informatics*, 78 (2009) 230-238
5) Von Hardenberg, J., Schwartz, M., Werner, T., Fuxius, S., Muller, M., Bolenz, C., . . . Heinrich, E. (2016). Influence of abiraterone acetate on circulating neuromediators in chemotherapy-naïve castration-resistant prostate cancer. *The Prostate,* 1-7. Retrieved February 2, 2016.
6) Andrade, S., Kahler, K., Frech, F., & Chan, K. (2006). Methods for evaluation of medication adherence and persistence using automated databases. Pharmacoepidemiology and Drug Safety, 15, 565-574. Retrieved May 4, 2015.

TABLES AND FIGURES

Table 1

	Control	RxTimerCap
Age at Enrollment (*average years*)	**76.7**	**74.0**
Gender	***Male: 100% (n = 19)*** ***Female: 0%***	***Male: 100% (n = 7)*** ***Female: 0%***
Ethnicity (%)	***White: 58%*** ***Hispanic: 10.5%*** ***African-American: 0%*** ***Asian: 10.5%*** ***Unknown: 21%***	***White: 72%*** ***Hispanic: 0%*** ***African-American: 0%*** ***Asian: 14%*** ***Unknown: 14%***

Table 2

t- test analysis

	Control	RxTimerCap
Number of Patients	**19**	**7**
MPR	***Mean: 1.02*** ***SD: 0.14***	***Mean: 1.07*** ***SD: 0.15***
Two-tail T-test between intervention and control group	***0.50***	

Table 3

Mann-Whitney U test

	Control	RxTimerCap	
Duration on Therapy (average days)	**81.4**	**106**	
Duration on Therapy (median days)	**68.0**	**117**	
p = 0.20 (median); not significant (p<0.05)			
Reason Patients Stopped Therapy (n = 8)			
Control Group			
Patient Deceased	**Switched Therapy**	**Unknown**	**Stopped Using Pharmacy**
1	**3**	**3**	**1**

TABLE 4: SURVEY RESPONSES

	Agree	Disagree	No response
I experienced problems when using the timer cap.	**1**	**3**	**3**
It was easy to set-up the timer cap.	**4**	**0**	**3**
The timer cap made it easier to remember when to take my medications.	**2**	. **1**	**4**
I would recommend the timer cap to others needing help in remembering to take their medications.	**4**	**0**	**3**
I used the timer cap throughout the entire study period.	**3**	**1**	**3**
It was easy to transfer the timer cap to another bottle.	**2**	**1**	**4**

APPENDICES

Data Dictionary:

- ID1- Subject number
- GRP2 – Intervention Group = 1 or Control Group = 2
- IFD3 - Initial Fill Date
- LFD4 - Last Fill Date
- TDS5 - Total Day Supply Dispensed
- LDS6 - Last Rx Day Supply
- TF7 - Total Number of Fills
- MPR8 - Mean Possession Ratio
- LOT9 - Length of Therapy (days)
- AGE10 - Age in Years at Time of Enrollment
- ETH11 - White (Non-Hispanic) = 1, Hispanic = 2, African-American = 3, Asian = 4

MPR calculation

- MPR: TDS5 / (LFD4 - IFD3) + LDS6

$$MPR = \frac{Total\ Rx\ Supply\ (days)}{last\ Rx\ date - first\ Rx\ date + last\ Rx\ day\ supply}$$

Questionnaire

1) I experienced problems when using the timer cap.
    a. Agree or Disagree
2) It was easy to set-up the timer cap.
    a. Agree or Disagree
3) The timer cap made it easier to remember when to take my medications.
    a. Agree or Disagree
4) I would recommend the timer cap to others needing help in remembering to take their medications.
    a. Agree or Disagree
5) I used the timer cap throughout the entire study period.
    a. Agree or Disagree
6) It was easy to transfer the timer cap to another bottle.
    a. Agree or Disagree

Data Collection Form

	A	B	C	D	E	F	G	H	I	J	K	L	M	N
1	ID1	Avella ID#	GRP2	Counseled?	Reason for D/C	IFD3	LFD4	TDS5	LDS6	TF7	MPR8	LOT9	AGE10	ETH11
2			Intervention=1, control=2			Initial Fill Date	Last Fill Date	Total Day Supply	Last Rx Day Supply	Total # fills	Mean Possession Ratio	Length on therapy (days)	Age (years) at time of enrollment	Ethnicity= White=1, Hispanic= 2, African American=3 , Asian=4
3	1													
4	2													
5	3													
6	4													
7	5													
8	6													
9	7													
10	8													
11	9													
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