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Original Article

Tolvaptan in Hospitalized Cancer Patients With Hyponatremia

A Double-Blind, Randomized, Placebo-Controlled Clinical Trial on Efficacy and Safety

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BACKGROUND: The rate of hyponatremia is higher in hospitalized cancer patients than in hospitalized patients without cancer and is associated with poor clinical outcomes. The availability of V_2 receptor antagonists has been a major breakthrough in the management of hyponatremia, but its efficacy and safety in treating hyponatremia in patients with cancer is not known. **METHODS:** Adult patients with cancer who were admitted to The University of Texas MD Anderson Cancer Center with nonhypovolemic hyponatremia (125-130 mmol/L) were randomized to receive either tolvaptan or placebo in a double-blind, placebo-controlled, adaptive, randomized trial. Both groups received the standard of care for hyponatremia, except that patients were allowed to drink to thirst. **RESULTS:** A preplanned Data Safety Monitoring Board analysis of 30 of 48 randomized patients who completed the study revealed that the primary endpoint of hyponatremia correction was met by 16 of 17 patients who received tolvaptan and by 1 of 13 patients who received placebo (94% vs 8%; $P<.001$), which met the study stopping rule for superiority. The secondary endpoints between the tolvaptan and placebo groups (mean ± standard deviation) for length of stay (21 ± 15 days vs 26 ± 15 days, respectively) and change in the Mini-Mental State Examination score (−0.35 ± 1.66 vs 0.31 ± 2.42, respectively) were not significantly different. No overcorrection of serum sodium (>12 mmol/L per day) was noted in the tolvaptan group, and the main adverse events noted were dry mouth, polydipsia, and polyuria, leading to 13% study withdrawal. **CONCLUSIONS:** Although tolvaptan was effective for correcting hyponatremia in patients with cancer, studies with a larger sample size will be required to confirm the current findings, including the outcomes of secondary endpoints. ***Cancer* 2014;120:744–51.** © *2013 American Cancer Society*.

KEYWORDS: hyponatremia, cancer, onconephrology, randomized controlled trial, V_2-receptor antagonists, tolvaptan.

INTRODUCTION

Hyponatremia is a common electrolyte abnormality in hospitalized patients, and its incidence is higher in those hospitalized patients who have cancer (nearly 1 in 2).[1-3] Hyponatremia, compared with eunatremia, in hospitalized cancer patients is associated with higher mortality rates, longer hospital stays, and higher hospital bills.[3] In patients with cancer, the arginine vasopressin (AVP) hormone, especially the ectopic type, plays an important role in the pathogenesis of hyponatremia.[4,5] The binding of AVP to its V_2 receptors on the basolateral side of the collecting tubules leads to the insertion of aquaporin-2 on the apical side, promoting water reabsorption. The results from trials to determine whether V_2-receptor antagonism can correct hyponatremia support the role of the AVP-V_2 receptor interaction in clinical settings of hyponatremia.[6,7] However, very few patients with cancer were included in those trials.[6,7] This is of concern, because the standard of care of severe fluid restriction is impractical in cancer patients who are receiving chemotherapy or undergoing stem cell transplantation. Of also of concern is the safety and biocompatibility of V_2 receptor antagonists in patients with cancer who receive several medications. Moreover, hyponatremia in patients with cancer can be associated with mental status alterations and poor clinical outcomes. Therefore, the primary objective of this study was to assess the safety and efficacy of tolvaptan—a relatively new and orally active nonpeptide antagonist of V_2 receptors—for correcting hyponatremia in cancer patients along with the secondary objectives of assessing the effect of tolvaptan on mental status and length of hospital stay.

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Additional Supporting Information may be found in the online version of this article.

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MATERIALS AND METHODS

The study approved by the Institutional Review Board (IRB) of The University of Texas MD Anderson Cancer Center, Houston, Texas (MD Anderson) was a double-blind, placebo-controlled, phase 3 trial of 14 days' duration that was conducted between May 2011 and July 2012 at MD Anderson. The IRB requires a 30-day follow-up for all clinical studies. We collected serum sodium values when available on day 30. The primary objective was to compare the rate of tolvaptan-treated correction of hyponatremia with that of placebo on day 14. Both the tolvaptan group the placebo group received the standard of care for hyponatremia except that drinking water to thirst was allowed. Adverse events were prospectively monitored and recorded. The secondary objectives were to compare the length of hospital stay and the change in mental test scores between the tolvaptan-treated and placebo groups. For study design, we chose the Bayesian adaptive randomization for its several reported useful features.[8] This was a registered clinical trial (clinicaltrials.gov identifier NCT01199198; randomized placebo-controlled trial of tolvaptan in hyponatremic patients with cancer).

Our analysis revealed that, with a minimum of 30 patients and a maximum of 120 patients, the operating characteristics yielded desirable properties when assuming a serum sodium correction rate of 25% (from published data[6]) in the control arm. For example, simulations revealed that, if the true serum sodium correction rate was 25% in the control arm and 65% in the tolvaptan arm, then the power to detect the superiority of tolvaptan would be 93% if all 120 planned patients were treated (see Supporting Table 1). The study was designed in 2 phases. In the run-in phase, patients would be randomly assigned at a 1:1 ratio to each arm until 30 evaluable patients completed the study. At that point, the first interim assessment would be conducted by the study statistician for the MD Anderson Data Safety Monitoring Board. If the probability that the correction rate, for example, in the tolvaptan arm, was greater than the rate in the control arm, given data that are > 0.975, then the trial would stop, and the tolvaptan arm would be selected as superior. Similarly, a futility rule, if the data favored placebo, also was in place. Once the efficacy data on first 30 evaluable patients became available, the adaptive phase of the study would start, in which more patients would be assigned to the arm that exhibited a higher rate of meeting the primary endpoint of serum sodium correction by day 14.

The full details on the operating characteristics of the design (Supporting Table 1); the study protocol and the study stopping rules for efficacy, futility, and toxicity (Supporting Table 2); and details on the implementation of the protocol are provided in the supporting materials for the web-only section. Briefly, adult patients with cancer who were admitted to MD Anderson and met the eligibility criteria for nonhypovolemic hyponatremia (125 to 130 mmol/L serum sodium) were recruited. One of the inclusion criteria was that patients had to have an Eastern Cooperative Oncology Group (ECOG) performance status from 0 (fully active) to 3 (capable of only limited self-care and confined to bed or chair $\geq$50% of waking hours).[9] The main exclusion criteria were correctable hyponatremia, admission to the critical care unit, the presence of renal failure (a glomerular filtration rate < 25 mL per minute), and receiving strong cytochrome P450 3A4 (CYP3A4) modulators. Once a patient was recruited, baseline measurements were taken. The Mini-Mental State Examination (MMSE), a simplified and validated test instrument used to assess for dementia, was administered by the research coordinator to score cognitive function at the beginning (before study drug administration) and at the end (day 14) of the study.[10,11] The score was obtained at baseline for all 48 randomized patients and for all 30 patients who completed the study.

Otsuka America Pharmaceuticals, Inc. (Rockville, Md) provided tolvaptan in 15-mg strength along with matching placebo tablets. All study patients received the standard of care for hyponatremia, which included fluid restriction to 1.5 L and, if indicated, salt tablets, diuretics, or a combination. To reduce the potential risk of sodium overcorrection, "drink-to-thirst" was allowed. The study tablet was titrated up to a maximum of 4 tablets (60 mg) to obtain a serum sodium correction of 6 to 12 mmol/L per day, targeting for a sodium level $\geq$136 mmol/L. The dose was continued for 14 days to maintain serum sodium levels between 136 and147 mmol/L. On day 14, baseline measurements were repeated, and the serum sodium level on day 14 was entered into the MD Anderson Clinical Trial Conduct website. The patients and investigators were kept blinded to treatment assignment. Adverse events were monitored and recorded to assess the clinical safety of tolvaptan. Version 3.0 of Common Terminology Criteria for Adverse Events (CTCAE) was used to grade the severity of adverse events (a grade $\geq$3 in the range from 0 to 5 was considered severe).

Sodium was measured using the VITROS method (VITROS Chemistry and Immunodiagnostic Products; Ortho Clinical Diagnostic, Inc., Raritan, NJ). The intra-assay and interassay coefficients of variation for sodium were 0.5 mEq/L and 0.7 mEq/L, respectively. The principal investigator (PI) was solely responsible for the study

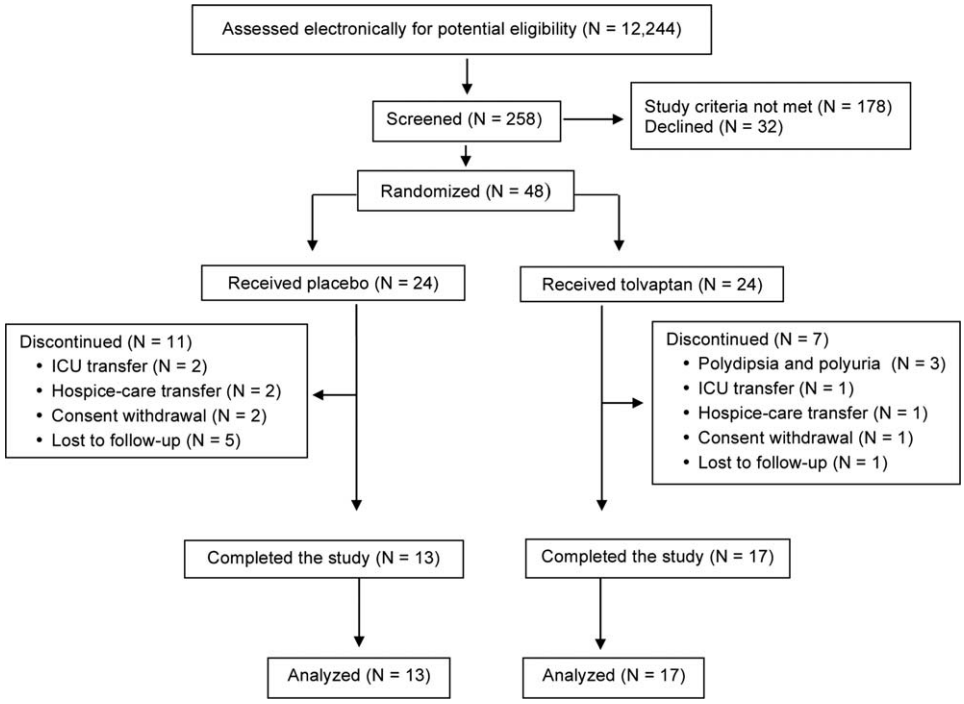


Figure 1. This is a flow diagram of the study details. ICU indicates intensive-care unit.

concept, and the PI (A.K.S.) and coinvestigators were responsible for protocol development, study performance, data analysis, and article preparation. The funding agency played no role in these activities. The PI assumes responsibility for the content and integrity of the study, and all authors attest to the accuracy and completeness of the reported data. The data are available for analysis.

Statistical Analysis

Demographics were tabulated using descriptive statistics and were compared using the Fisher exact test for categorical variables and the *t* test or the Mann-Whitney *U* test for continuous variables. A 2-tailed *P* value $\leq .05$ was considered statistically significant. The proportions of patients who achieved the primary endpoints on day 14 in each group were compared. The mean serum sodium levels between the placebo and tolvaptan groups were compared at 4 time points (baseline, day 7, day 14, and day 45) using an analysis of variance along with post hoc Bonferroni correction for 4 pairwise comparisons; for these analyses, only *P* values $< .0125$ were considered significant. To address the issue of patients who dropped out of the study, the following sensitivity analyses (for details, see the supporting materials in the web-only section) were undertaken: 1) using the overall hypernatremia correction rate for evaluable patients to impute response for those who dropped out; 2) reanalyzing data from patients in the placebo arm who did not complete the trial by using a what-if scenario, which assumed that the patients who dropped out had completed the trial and were responders; and 3) using a model-based approach to impute hyponatremia correction for dropouts based on baseline patient characteristics (ECOG performance status, age, baseline serum sodium level, and body weight) and observed responses in the evaluable patients.[12]

Deaths that occurred during the 14-day study period and the 30-day follow-up period (45 days from the start of the study) were recorded, and the proportion of patients who died was compared between the 2 groups using the Fisher exact test. Statistical analyses of the study were undertaken independently and were verified by 2 authors (A.K.S. and S.P.) who used the statistical software programs SPSS 19 (SPSS, Inc., Chicago, Ill) and SAS 9.3 (SAS Institute, Inc., Cary, NC).

RESULTS

Patient Population

Of 258 screened patients, 48 were randomized (24 patients to the placebo arm and 24 patients to the tolvaptan arm) (Fig. 1). On the basis of study entry data on volume status and serum and urine electrolytes and

TABLE 1. Baseline Demographics and Clinical Characteristics of Patients in the Placebo Group and the Tolvaptan Group who Completed the 14-Day Study

Characteristic	Median (Range)[a]		P[b]
	Placebo Group, N = 13	Tolvaptan Group, N = 17	
Age, y	60 (36-60)	69 (52-81)	<.05
Sex, % of men	54	53	.66
Cancer diagnosis, % of patients[c]			
Solid tumors	69	65	.58
Liquid tumors[d]	31	35	.52
Chemotherapy, % of patients	38	47	.644
Body weight, kg	67 (47-125)	79 (49-115)	.62
ECOG score, % of patients			
1	8	29	.31
2	39	35	
3	53	36	
MMSE score[e]	15 (7-16)	14 (9-16)	.74
Fluid intake, l/d	1.86 (0.70-3.80)	1089 (0.84-3.90)	.59
Hct, %	30 (26-39)	30 (26-36)	.60
Blood glucose, mg/dL	102 (66-180)	104 (79-178)	.76
Serum creatinine, mg/dL	0.56 (0.42-0.86)	0.74 (0.42-1.16)	<.05
Serum sodium, mmol/L	129 (126-130)	129 (125-130)	.70
Serum osmolality, mosm/kg	272 (260-279)	275 (244-279)	.43
Urine sodium, mmol/L	99 (48-151)	91 (42-149)	.59
Urine osmolality, mosm/kg	394 (252-725)	415 (242-831)	.96

Abbreviations: ECOG, Eastern Cooperative Oncology Group; Hct, hematocrit; MMSE, Mini-Mental State Examination.
[a] Data are presented as medians and ranges except where noted as the percentage of patients.
[b] Data data reported as medians and ranges were analyzed with the Mann-Whitney *U* test, and data presented as percentages were analyzed using the Fisher exact test.
[c] Details on the specific cancer diagnosis are provided in the text (see Results).
[d] Liquid tumors included leukemia, lymphoma, and myeloma.
[e] All correct answers produced a maximum score of 16.

osmolality (aggregate data are provided in Tables 1 and 2), all patients who were recruited to this study had evidence for antidiuretic hormone-dependent hyponatremia, and most were hypervolemic. Approximately 11% of patients were euvolemic and may have had the syndrome of inappropriate antidiuretic hormone secretion. The numbers of patients in the placebo and tolvaptan groups according to specific cancer type were as follows: lung cancer, 3 patients and 4 patients in the placebo and tolvaptan groups, respectively; brain tumor, 2 patients in each group; leukemia, 0 patients and 5 patients, respectively; sarcoma, 5 patients and 0 patients, respectively; uterine cancer, 0 patients and 2 patients, respectively; lymphoma, 4 patients and 3 patients, respectively; melanoma, 2 patients in each group; pancreatic cancer, 0 patients and 1 patient, respectively; cholangiocarcinoma, 1 patient and 0 patients, respectively; hepatocellular cancer, 0 patients and 1 patient, respectively; multiple myeloma, 2 patients and 0 patients, respectively; thyroid cancer, 1 patient and 0 patients, respectively; ovarian cancer, 0 patients and 1 patient, respectively; renal cell carcinoma, 1 patient in each group; esophageal cancer, 1 patient and 0 patients, respectively; rectal cancer, 1 patient and 2 patients, respectively; and Paget disease of the scrotum, 1 patient and 0 patients, respectively. No overall statistical difference was observed in the tumor type distribution ($P = 0.33$). Eleven patients in the placebo group and 7 patients in the tolvaptan group discontinued the study for the reasons noted in Figure 1.

Baseline Characteristics

Table 1 provides baseline characteristics of the patients who completed the study. ECOG performance status did not differ statistically between the tolvaptan and placebo groups, but the mean age was significantly younger in the placebo group (Table 1). The baseline demographic and clinical characteristic for all patients were compared between those randomized to placebo (N = 24) and to tolvaptan (N = 24) (see Supporting Table 3). All variables were comparable between the groups except for ECOG performance status. The placebo group included significantly more patients with higher ECOG scores than the tolvaptan group. In Supporting Table 4, the baseline characteristics of patients who did not complete the study (N = 18) are compared with the characteristics of those who completed the study (N = 30). None of the variables

TABLE 2. Measurements in the Placebo and Tolvaptan Groups During the 14-Day Study Period

Variable	Median (Range)[a]		P[b]
	Placebo Group, N = 13	Tolvaptan Group, N = 17	
Change in body weight, kg	−5.4 (−16.8 to 3.2)	−2 (−2.40 to 2.40)	.76
Change in HCT, %	2.20 (−6.10 to 7.60)	3.30 (−4.50 to 11.80)	.70
Change in serum bilirubin, mg/dL	0.00 (−0.20 to 0.60	0.00 (−16.30 to 4.40)	.56
Change in ALT, units/L	5 (−5 to 21)	−17 (−94 to 388)	.69
Change in AST, units/L	1 (−8 to 10)	−4 (−81 to 501)	.57
Change in serum creatinine, mg/dL	0.05 (−0.19 to 0.38)	0.04 (0.27-1.39)	.35
Change in blood glucose, mg/dL	−6 (−53 to 31)	3 (−87 to 206)	.35
Change in serum sodium, mmol/L	3 (−2 to 9)	10 (6-14)	< .01
Change in serum osmolality, mosm/kg	4 (−16 to 21)	16 (3-61)	< .01
Fluid intake on d 3, L/d	2.25 (1.01-4.0)	2.35 (1.04-5.20)	.83
Urine output on d 3, L/d	2.01, 0.60 to 2.56	2.60 (1.8-5.56)	0.08
Change in MMSE score	0.0 (−3 to 6)	0.0 (−4 to 2)	.41
Length of hospital stay, d	28 (2-51)	18 (3-50)	.36
Death, % of randomized patients[c]	38	45	.57
Use of salt tablets, % of patients	39	29	.60
Use of diuretics, % of patients	62	53	.64
Use of salt tablets and diuretics, % of patients	15	17	.87
No. of maximum study tablets prescribed per day, tablets	4 (2-4)	3 (1-4)	.06
Total study tablets taken, Mean ± SD percentage of prescribed	94.0 ± 6.0	96.0 ± 6.0	.86

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HCT, hematocrit; MMSE, Mini-Mental State Examination; SD, standard deviation.

[a] Data are presented as medians and ranges except where noted as the percentage of patients or the mean ± SD.

[b] Data reported as medians and ranges were analyzed using the Mann-Whitney *U* test, and data presented as percentages were analyzed using the Fisher exact test.

[c] Death was reported up to 30 days of follow-up (ie, a total of 45 days after the start of the study).

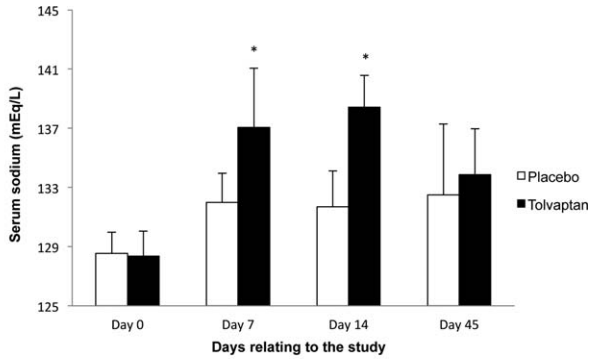
differed between the 2 groups, including ECOG scores (see Supporting Table 4). Finally, Supporting Table 5 provides data comparing patients in the placebo group with patients in the tolvaptan group who did not complete the study. None of the variables differed between the groups, except that there were significantly more patients with higher ECOG scores in the placebo group.

Compliance With Study Medication and Cointerventions With Other Drugs

All patients received the allocated treatment. There were no protocol changes without prior IRB approval. Noncompliance with protocol was limited to 20% of patients not returning the medications. Medication compliance was similar in both groups at approximately 95%. The use of salt tablets and diuretics did not differ significantly, although fewer patients who received tolvaptan had received salt and diuretic treatment (Table 2). Specifically, the use of furosemide was 61% in the placebo group and 53% in the tolvaptan group. The average daily dose of furosemide was approximately 40 mg daily per patient in both groups. Thirty percent of patients in each group already were receiving furosemide at the start of the study, and furosemide was initiated in an additional 30% of patients in the placebo group and in an additional 29% of patients in the tolvaptan group during the study.

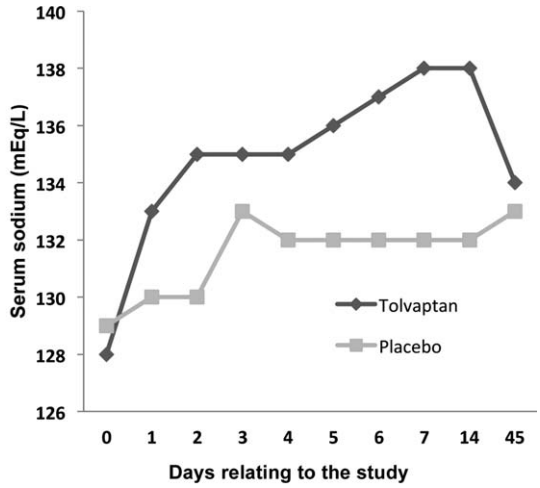
Comparison of Groups for Primary Outcome

During the first planned Data Safety Monitoring Board meeting, data on 30 patients who completed the study (13 in the placebo group and 17 in the tolvaptan group) were analyzed. Most baseline characteristics of patients in the 2 groups were comparable (Table 1). Sixteen of 17 patients in the tolvaptan group and 1 of 13 patients in the placebo group achieved the primary endpoint of serum sodium correction on day 14 (94% vs 8%, respectively; $P < .001$). Thus, the study met the predefined stopping rule of superiority for tolvaptan over placebo; and, according to IRB instructions, further patient recruitment was halted. Figure 2 displays serum sodium levels at Day 0, Day 7, Day 14 and Day 45 in the two groups. Figure 3 shows that most of the increase in serum sodium occurred in the first few days of starting tolvaptan: the level increased slowly and significantly in the tolvaptan group from day 0 to day 14, but it decreased to placebo levels after tolvaptan was discontinued. In the placebo group, the mean serum sodium level increased slightly by day 7 (Fig. 3). By day 7, 11 of 17 patients in the tolvaptan group (65%) and 1 of 13 patients in the placebo group (8%) achieved eunatremia. The absolute change in serum sodium levels (± standard deviation) over 14 days was



N in placebo	13	13	13	8
N in tolvaptan	17	17	17	8

Figure 2. Serum sodium values (mean ± standard deviation) are illustrated for patients in the placebo group and the tolvaptan group on days 0, 7, 14, and 45 of the study. All available values are included. Day 45 represents the time point 30 days after the study tablets were stopped. An asterisk indicates $P < .001$ versus placebo.



N in placebo	13	13	12	11	9	9	9	13	13	8
N in tolvaptan	17	17	15	14	12	10	10	17	17	8

Figure 3. Sequential serum sodium values are illustrated for patients in the tolvaptan group and the placebo group who completed the study. All available values are included. Day 45 represents the time point 30 days after the study tablets were stopped.

10.17 ± 2.45 mmol/L in the tolvaptan group and 3.92 ± 2.53 mmol/L in the placebo group ($P < .001$).

Table 2 provides key measurements taken during the 14 days of the study in patients who completed the study. The increase in the serum osmolality level, as in the serum sodium level, was significantly higher in the tolvaptan group than in the placebo group (Table 2). Urine output on day 3 was higher and the length of hospital stay was shorter in the tolvaptan group, but neither difference reached statistical significance. Changes in bodyweight, hematocrit, serum bilirubin, alanine transaminase, aspartate transaminase, creatinine, and blood glucose during the 14 days were not significantly different between the groups (Table 2).

Comparison of Groups for Secondary Outcomes

The secondary endpoints between the tolvaptan and placebo groups (mean ± standard deviation) for length of stay (21 ± 15 days vs 26 ± 15 days, respectively) and changes in the MMSE score (−0.35 ± 1.66 vs 0.31 ± 2.42, respectively) were not significantly different (Table 2).

Sensitivity Analysis

By using the overall hypernatremia correction rate (17 of 30 patients; 56.6%) of evaluable patients to impute response for the patients who dropped out, there remained a statistically significant treatment effect ($P < .001$). Four more patients in the placebo arm did not complete the trial; thus, using a what-if scenario, we reanalyzed the primary endpoint assuming that these patients had been responders. A significantly high rate of serum sodium correction still was noted in the tolvaptan group ($P < .001$). Similarly, when we used a model-based approach to impute hypernatremia correction for dropouts using baseline patient characteristics (ECOG performance status, age, baseline serum sodium level, and body weight) and the observed responses in the evaluable patients, a statistically significant treatment effect remained ($P = .001$). More details of the sensitivity analyses and results are presented in the web-only section.

Safety

The common adverse events unique to the tolvaptan group were dry mouth (21%), thirst (46%), and increased urination (frequency and volume; 13%) (see Supporting Table 6). Thirteen percent of patients who were receiving tolvaptan and who had these symptoms at grade 2 or 3 CTCAE levels withdrew from the study. The common (≥5%) adverse events were pain (of any type), nausea, vomiting, edema, and infections (of any type). The serious adverse events (CTCAE grade ≥3) were pneumonia, respiratory failure, hypotension, and worsening of edema. The frequencies of these serious adverse events were not increased in the tolvaptan group (see Supporting Table 6), and there were no significant differences in 45-day mortality between the 2 groups (Table 2).

DISCUSSION

This controlled trial demonstrated that 14 days of tolvaptan therapy achieved a 94% rate of hyponatremia correction

compared with an 8% rate in the placebo arm while both groups were receiving the standard of care. The mental state and the length of hospital stay did not differ significantly between the groups. The short-term use of tolvaptan was not associated with any increased adverse events other than dry mouth, polyuria, and polydipsia.

For this study, we chose to use the adaptive randomization approach rather than the frequentist randomization approach, because the former could have allowed us to use observed results in preceding patients to base assignment probabilities. However, early termination of the study based on the first preplanned Data Safety Monitoring Board analysis obviated the need for the adaptive phase of randomization. Despite stopping early, our analyses, including the intention-to-treat analysis, suggested the superiority of tolvaptan over placebo in correcting hyponatremia in cancer patients. The correction afforded by the commonly used clinical strategies of modest fluid restriction, salt tablets, and/or diuretics was incomplete (see Figs. 2 and 3). The correction in the tolvaptan group was evident from the first day of its use; the majority of patients achieved eunatremia by day 7, and nearly all achieved eunatremia by day 14. No patients experienced an overcorrection of hyponatremia in this study. Although the study was initiated in the hospital to watch for overcorrection, our data suggested (but do not demonstrate) that tolvaptan could be initiated safely in outpatients, especially if it was started at a lower dose of 7.5 mg and if patients were allowed to drink to thirst.

The cyp3A4 enzyme system, which is responsible for metabolizing tolvaptan, also handles other drugs, including anticancer drugs.[13] Although, in the current study, we excluded patients who were receiving strong cyp3A4 compounds, such as azoles, for potential safety concerns, most patients were receiving multiple drugs, and nearly half were receiving chemotherapeutic drugs. Although we did not have any clinical or laboratory evidence of potential interactions between tolvaptan and other drugs or of toxicity from such interactions, it is prudent to continue to look for possible interactions. Tolvaptan was associated with a higher incidence of hyperglycemia in 1 study[6] and with elevations of serum alanine transaminase and aspartate transaminase levels in another study.[14] The US Food and Drug Administration has determined that the drug tolvaptan should not be taken for longer than 30 days and should not be used in patients who have underlying liver disease. Our study was of shorter duration and used lower doses compared with other studies. Therefore, we could not fully evaluate the adverse findings associated with longer term use of tolvaptan.

An important issue that we had addressed in this study was the occurrence of missing data in our dropout participants. In an intention-to-treat analysis approach, we imputed the missing data in 1 of the sensitivity analyses, yet we still observed that tolvaptan was effective in correcting serum sodium. In our study, the ECOG score was higher in the placebo group than in the tolvaptan group, possibly explaining the higher dropout rate in the placebo group. However, we observed that tolvaptan was still efficacious after adjusting for ECOG values in the model-based sensitivity analysis.

Despite the fluid allowance for patients to drink-to-thirst in this study, the serum sodium level in patients who received tolvaptan was corrected and remained corrected until the end of the study in all but 1 patient (who had a serum sodium level of 135 mmol/L on day 14). We chose not to use improvement of symptoms, such as headache and nausea, as an outcome measurement, because these symptoms can be nonspecific in patients with cancer who are receiving chemotherapy. Instead, we sequentially measured any changes in cognitive function by using a questionnaire that had been validated primarily in patients with dementia. No significant change was observed before or after tolvaptan. Most of our patients had chronic hyponatremia, probably allowing neurocognitive adaptation. The duration of hospital stay in the patients who received tolvaptan also was not significantly lower, possibly because none of our patients were admitted to the hospital for the purpose of correcting of hyponatremia per se. Also, the study was powered to test the primary endpoint of efficacy and safety of tolvaptan in cancer patients and not the secondary endpoints. However, in the absence of a significant difference in the 2 clinical outcomes, the actual clinical value of the increases in serum sodium in the tolvaptan-treated population is currently not clear.

The results of our study should be considered preliminary; thus, before the wider use of tolvaptan or other expensive V2-receptor antagonists, studies with larger sample sizes will be required to demonstrate that hyponatremia correction improves outcomes. For example, this may require studies in symptomatic patients with significant hyponatremia or studies conducted in unique areas, such as the emergency department, in which acute, supervised treatment of hyponatremia with tolvaptan may reduce hospitalization for correcting hyponatremia with substantial cost benefit. Anecdotally, moderate to severe hyponatremia in our cancer patients has delayed cancer treatments (chemotherapy, stem cell transplantation, and surgeries) and hospital discharges and has prompted hospital admissions and critical care transfers.

In summary, this randomized controlled trial demonstrates that tolvaptan is effective in correcting hyponatremia among patients with cancer. Main adverse effects are thirst, polyuria, and polydipsia. In patients who have cancer with nonhypovolemic hyponatremia of moderate severity and do not respond to standard-of-care treatment for hyponatremia, tolvaptan can be an effective treatment for correcting hyponatremia.

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CONFLICT OF INTEREST DISCLOSURES

Dr. Salahudeen has received financial compensation in the form of honorarium for a lecture and a fee for attending 1 medical board meeting.

REFERENCES

1. Anderson RJ. Hospital-associated hyponatremia. *Kidney Int*. 1986; 29:1237-1247.
2. Upadhyay A, Jaber BL, Madias NE. Epidemiology of hyponatremia. *Semin Nephrol*. 2009;29:227-238.
3. Doshi SM, Shah P, Lei X, et al. Hyponatremia in hospitalized cancer patients and its impact on clinical outcomes. *Am J Kid Dis*. 2012;59:222-228.
4. Schrier RW. Water and sodium retention in edematous disorders: role of vasopressin and aldosterone. *Am J Med*. 2006;119:S47-S53.
5. Adrogue HJ, Madias NE. Hyponatremia. *N Engl J Med*. 2000;342: 1581-1589.
6. Schrier RW, Gross P, Gheorghiade M, et al. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. *N Engl J Med*. 2006;355:2099-2112.
7. Ghali JK, Koren MJ, Taylor JR, et al. Efficacy and safety of oral conivaptan: a V1A/V2 vasopressin receptor antagonist, assessed in a randomized, placebo-controlled trial in patients with euvolemic or hypervolemic hyponatremia. *J Clin Endocrinol Metab*. 2006;91:2145-2152.
8. Berry DA. Bayesian clinical trials. *Nat Rev Drug Discov*. 2006;5:27-36.
9. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5:649-655.
10. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189-198.
11. Tombaugh TN. Test-retest reliable coefficients and 5-year change scores for the MMSE and 3MS. *Arch Clin Neuropsychol*. 2005;20: 485-503.
12. Rubin DB. Multiple imputation after 18+ years. *J Am Stat Assoc*. 1996;91:473-489.
13. Kivisto KT, Kroemer HK, Eichelbaum M. The role of human cytochrome P450 enzymes in the metabolism of anticancer agents: implications for drug interactions. *Br J Clin Pharmacol*. 1995;40:523-530.
14. Torres VE, Chapman AB, Devuyst O, et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. *N Engl Med*. 2012;367:2407-2241.