Original Study

Folic Acid Reduces Mucositis in Metastatic Renal Cell Carcinoma Patients: A Retrospective Study

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Abstract

Mucositis is a frequent side effect of targeted therapy in metastatic renal cell carcinoma (mRCC) patients, which leads to dose reduction, discontinuation, or treatment shift. In this retrospective study of 77 patients, we found folic acid to significantly reduce mucositis in mRCC patients receiving systemic therapy. Patient outcomes were equal or better than expected. A double-blind, placebo-controlled prospective study is ongoing (NCT03581773) in order to validate this finding.

Background: Mucositis is often experienced in metastatic renal cell carcinoma (mRCC) patients treated with targeted therapies. This might impair daily quality of life and lead to dose reduction, discontinuation, or treatment shift. We assessed the effect of folic acid to reduce mucositis. **Patients and Methods:** Patients treated with systemic therapy for mRCC who developed Grade ≥2 mucositis according to Common Terminology Criteria for Adverse Events version 4.0 (CTCAE) received oral folic acid to reduce mucositis. The medical charts were retrospectively reviewed. **Results:** A total of 77 patients had Grade ≥2 mucositis during therapy with sunitinib (n = 29), pazopanib (n = 24), everolimus (n = 10), axitinib (n = 4), temsirolimus (n = 3), interleukin-2/interferon-α (n = 3), cabozantinib (n = 2), bevacizumab (n = 1), and nivolumab (n = 1). Given in doses of 1 to 5 mg daily, folic acid significantly reduced mucositis, mean CTCAE grade 0.88 (95% confidence interval [CI], 0.74-1.03) versus 2.38 (95% CI, 2.26-2.54; $P < .0001$). Stratified according to treatment, folic acid significantly reduced mucositis grade for sunitinib (0.97 [95% CI, 0.75-1.18] vs. 2.45 [95% CI, 2.23-2.67], $P < .0001$), pazopanib (0.96 [95% CI, 0.67-1.25] vs. 2.20 [2.03-2.38], $P < .0001$), everolimus (0.60 [95% CI, 0.10-1.10] vs. 2.60 [95% CI, 2.23-2.97], $P < .0001$), and other treatments (0.79 [95% CI, 0.38-1.19] vs. 2.36 [95% CI, 2.07-2.64], $P < .0001$). Of the 77 patients, 8 (10%) patients received dose reduction. Overall progression-free survival was 14 months and overall survival was 31 months. **Conclusion:** Folic acid reduced mucositis in mRCC patients receiving systemic therapy. This finding needs prospective validation. A double-blind, placebo-controlled prospective evaluation of folic acid is ongoing (NCT03581773).

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Keywords: Adverse events, Immunotherapy, Stomatitis, TKI, mTOR inhibitor

Introduction

Inactivation of von Hippel–Lindau tumor suppressor gene in kidney proximal nephron cells leads to excess production of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), resulting in excessive angiogenesis. This understanding of clear-cell renal-cell carcinoma basic genetic pathogenesis has led to the development and approval of new treatment modalities aimed at VEGF, PDGF, and mammalian target of rapamycin (mTOR) tyrosine kinase receptors, including sorafenib, sunitinib, pazopanib, axitinib, cabozantinib, tivozanib, lenvatinib, temsirolimus, and everolimus.[1] The clinical implementation within the last decennium of this large number of targeted therapies in patients with metastatic renal cell carcinoma (mRCC) has translated into improved survival.[2,3] Recently the checkpoint immunotherapies nivolumab and ipilimumab have added to the armamentarium.[4,5]

Tyrosine kinase inhibitors (TKIs) target VEGF and PDGF signaling pathways, by competitively binding to the receptor tyrosine kinases, thereby inhibiting signal transduction. TKIs also have effects on other kinases in an unspecific manner, and thereby exert adverse events.[6] Among the most common adverse events with TKI use are fatigue, loss of appetite, diarrhea, nausea, and mucositis.[6-8] Also, mTOR

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inhibitors are known for causing mucositis; a meta-analysis of everolimus adverse events reported nearly 70% of patients experienced oral mucositis to some extent.[9]

Patients receive TKI or mTOR inhibitors on a daily basis and life-long. Some adverse events require dose reduction, discontinuation, or shift of treatment. First-line therapies sunitinib and pazopanib are discontinued in 20% to 24% of patients because of toxicity and second-line therapies have similar discontinuation rates.[7,8] Toxicity might result in daily poor quality of life or frequent change of therapy, leading to a situation in which available drugs are depleted in a short time.

Oral mucositis has for many years been a frequent and significant adverse event to anticancer chemotherapy treatments. This has led to the understanding of mucositis as a 5-phase process involving DNA damage (phase 1), upregulation of transcription factors (phase 2), signaling and amplification (phase 3), ulceration (phase 4), and healing (phase 5).[10] The mucositis physiopathology for continuous targeted therapy is not well understood. Therefore, the main focus has been on oral hygiene care, diet modifications, and pain management.[11]

All human cell production requires folic acid, including mucosa cells. Folic acid is a B9-vitamine and is activated in vivo to tetrahydrofolic acid by dihydrofolate reductase (DHFR). To synthesize, repair, and methylate DNA, the human organism demands folic acid. This is especially important when there is rapid cell division and growth as in mucosa repair.[12] It is unknown whether the systemic mRCC treatments inhibit DHFR.

In this single-center retrospective study we report the effect of folic acid on mucositis in patients with mRCC treated with targeted therapy and immunotherapy.

Patients and Methods

The primary aim of this study was to evaluate the effect of folic acid on mucositis. A secondary aim was to characterize patient outcome with current standard of care in patients with mRCC. Data were collected through the mRCC database at Department of Oncology, Aarhus University Hospital, Denmark. The study cohort comprised data of 77 mRCC patients, who experienced Grade $\geq$2 mucositis (nasal, oral, pharyngeal, anal, or genital) from systemic therapy, treated with folic acid supplement from September 2013 to July 2016 with follow-up until August 2018. The study was approved by the Danish Data Protection Agency and the Danish Health Authority.

Baseline patient characteristics included demographic, clinicopathological, and laboratory data. Outcome data were retrospectively collected from medical chart reviews and electronic records. The folic acid supplement was initially given in small doses of 1 to 2 mg daily for safety reasons. Over time, it became increasingly clear that most patients required higher doses of folic acid to alleviate mucosal toxicity. We chose to dose-escalate folic acid to 5 mg daily (ie, 1 tablet daily) as a fixed dose, because this would simplify administration, and certify that as many patients as possible received sufficient amounts of folic acid.

The primary end point was changes in the mean degree of Common Terminology Criteria for Adverse Events version 4.0 (CTCAE)-graded mucositis before and after folic acid supplementation. The degree of mucositis was assessed according to CTCAE every 4 to 6 weeks. The registered symptoms included oral mucosal pain/hypersensitivity, dysgeusia, xerostomia, ulceration, nose bleeding, genital mucosal affection (glans penis, vagina, urethra), and rectal/anal mucosal affection.

Risk stratification was performed for all patients at first-line mRCC treatment initiation using the criteria of the Memorial Sloan Kettering Cancer Center (MSKCC).[13] The objective response rate was defined as the sum of complete and partial remissions according to Response Evaluation Criteria In Solid Tumors 1.1. Overall survival (OS) was defined as the time between systemic therapy initiation and the date of death or censoring on the day of the last follow-up visit. Progression-free survival (PFS) was defined as the period between treatment initiation and progression or death, with censoring at the last follow-up visit.

Stata 10.0 statistical analysis software (Stata Corp, College Station, TX) was used for calculation of mean-comparison test on paired data, Kaplan–Meier survival plots, and univariate Cox regression analysis. All *P* values were 2-sided.

Results

A total of 77 patients with mRCC who developed Grade $\geq$2 mucositis were included (Figure 1). Patients received treatment with sunitinib (n = 29), pazopanib (n = 24), everolimus (n = 10), axitinib (n = 4), temsirolimus (n = 3), interleukin-2 (IL-2)/interferon-α (IFN; n = 3), cabozantinib (n = 2), bevacizumab (n = 1), and nivolumab (n = 1). Treatment line while commencing folic acid supplement treatment was first-line, second-line, and third-line in 55 patients (72%), 16 (21%), and 5 (6%), respectively. The

Figure 1 Example of a Patient With Oral Mucositis

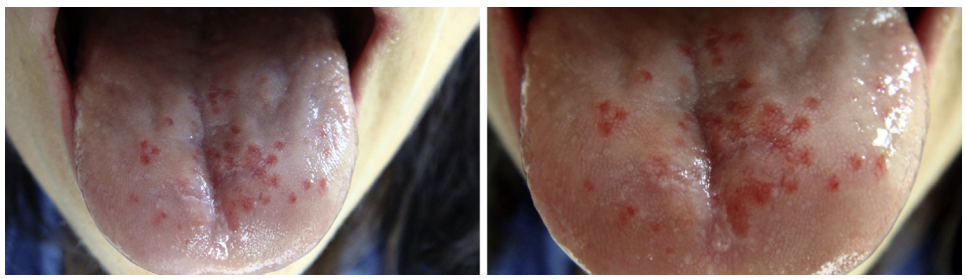


Table 1 Clinical and Histopathological Characteristics of the Patient Cohort

Clinical and Histopathological Characteristics	All Patients (n = 77)	Sunitinib-Treated Patients (n = 29)	Pazopanib-Treated Patients (n = 24)	Everolimus-Treated Patients (n = 10)	Other Treatments (n = 14)
Median Age at mRCC Diagnosis (Range)	63 (37-80)	66 (43-80)	65 (44-80)	56 (46-65)	55 (37-67)
Male-Female Ratio	1.48	1.64	1.67	1.50	1.00
Previous Nephrectomy, n (%)	66 (86)	28 (97)	18 (75)	9 (90)	11 (79)
MSKCC Prognostic Criteria at mRCC Treatment Initiation, n (%)					
Favorable	20 (26)	13 (45)	1 (4)	1 (10)	5 (36)
Intermediate	49 (64)	15 (52)	20 (83)	8 (80)	6 (43)
Poor	8 (10)	1 (3)	3 (13)	1 (10)	3 (21)
Treatment Line, n (%)[a]					
First	55 (72)	24 (83)	21 (88)		10 (71)
Second	16 (21)	4 (14)	1 (8)	7 (70)	3 (21)
Third	5 (6)	1 (3)	1 (4)	3 (30)	1 (8)
Fifth	1 (1)				1 (8)

Abbreviations: mRCC = metastatic renal cell carcinoma; MSKCC = Memorial Sloan Kettering Cancer Center.
[a]On the basis of the particular treatment received during folic acid supplementation.

median age was 63 years; 46 patients (60%) were male. A total of 66 (86%) had previous nephrectomy. Risk allocation according to MSKCC criteria were favorable in 20 patients (26%), intermediate in 49 (64%), and poor in 8 (10%). The median follow-up time was 31 (range, 1-114) months. Overall, a total of 56 patients (73%) progressed and 54 (70%) died (Table 1).

Of the 77 patients, 38 (49%) patients received folic acid dose <5 mg daily, the remaining were dose-escalated to or commenced at 5 mg daily. Patients reported an effect of folic acid within days to few weeks. Patients reached full effect of the folic acid supplementation in 31 days (median). Folic acid given in doses of 1 to 5 mg daily significantly reduced mucositis, mean CTCAE grade 0.88 (95% confidence interval [CI], 0.74-1.03) versus 2.38 (95% CI, 2.26-2.54; $P < .0001$; Table 2). Stratified according to treatment, folic acid supplementation significantly reduced mucositis grade for sunitinib (0.97 vs. 2.45; $P < .0001$), pazopanib (0.96 vs. 2.20; $P < .0001$), everolimus (0.60 vs. 2.60; $P < .0001$), and other treatments including IL-2 and nivolumab (0.79 vs. 2.36; $P < .0001$; Table 2 and Figure 2). Four patients were reintroduced with folic acid after a shift of systemic treatment because of disease progression, thereby experiencing the effect of folic acid across treatments. The folic acid administration was stopped simultaneously with discontinuation of the systemic therapy at time of progression, and not reintroduced until the patient experienced ≥2 mucositis during the next line of treatment. All 4 patients improved significantly in mucositis during first and second treatment after folic acid initiation.

Stratified according to MSKCC risk group allocation, was with no statistically significant difference in mucositis at the time of folic acid commencement; favorable risk group, 2.20 (95% CI, 1.96-2.44) versus intermediate risk group, 2.45 (95% CI, 2.30-2.59; $P = .069$), intermediate risk group versus poor risk group, 2.38 (95% CI, 1.94-2.81; $P = .702$) and favorable risk group versus poor risk group ($P = .430$).

A relationship between grade of stomatitis and efficacy was not seen. The degree of mucositis before folic acid supplementation (3 or 4 vs. 2) had no effect on either PFS or OS for all patients (Table 3).

Patient outcomes were not deteriorated with use of folic acid supplementation. Median PFS for all patients was 14 months (95% CI, 1-76 months). Stratified according to treatment, PFS for patients treated with sunitinib was 22 months, pazopanib 15 months, and everolimus 15 months. Median OS for all patients was 31 months (95% CI, 1-114 months). Stratified according to treatment OS for patients treated with sunitinib was 38 months, pazopanib 19 months, and everolimus 60 months (Table 4 and Figure 2).

Discussion

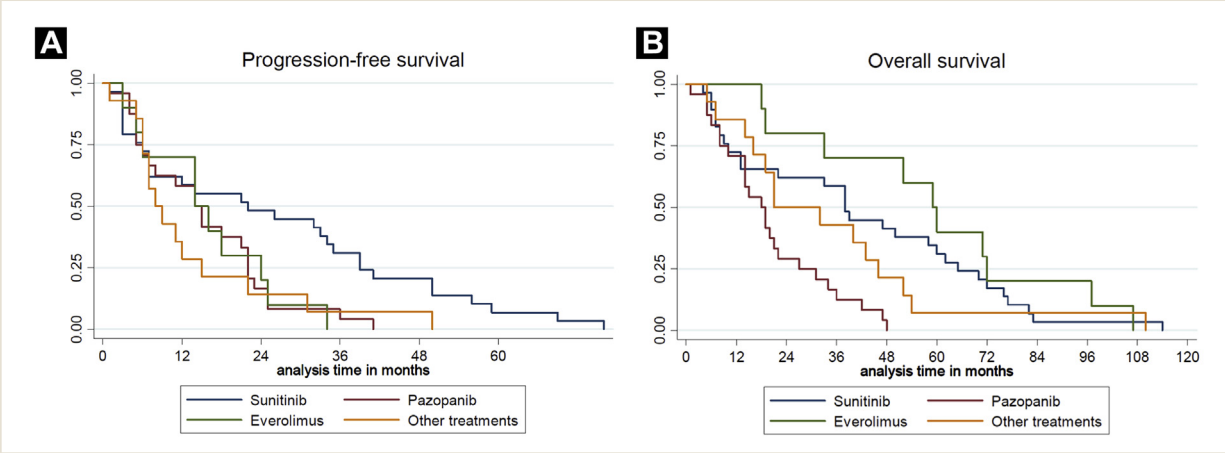
The present study represents, to our knowledge, the first documentation of a specific therapy to reduce mucositis developed

Table 2 Mean Mucositis Grading on the Basis of CTCAE. Before versus After Folic Acid Supplement Initiation

Mean CTCAE Mucositis Grading	All Patients (n = 77)	Sunitinib-Treated Patients (n = 29)	Pazopanib-Treated Patients (n = 24)	Everolimus-Treated Patients (n = 10)	Other Treatments (n = 14)
Before Folic Acid Administration	2.38 (2.26-2.54)	2.45 (2.23-2.67)	2.20 (2.03-2.38)	2.60 (2.23-2.97)	2.36 (2.07-2.64)
After Folic Acid Administration	0.88 (0.74-1.03)	0.97 (0.75-1.18)	0.96 (0.67-1.25)	0.60 (0.10-1.10)	0.79 (0.38-1.19)
P	<.0001	<.0001	<.0001	<.0001	<.0001

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events version 4.0.
Data are presented as HR (95% CI), except where otherwise noted.

Figure 2 Kaplan–Meier Survival Estimates Sorted According to Treatment. (A) Progression-Free Survival in the Examined Cohort. (B) Overall Survival in the Examined Cohort



during treatment with TKIs, mTOR inhibitors, or immunotherapies in patients with mRCC. Vitamin B9 folic acid significantly alleviated mucositis in these patients. Mucositis is often experienced in mRCC patients treated with contemporary therapy. Sunitinib treatment was initially reported with stomatitis in 25% of patients, mucosal inflammation in 20%, epistaxis in 12%, and dry mouth in 11%.[14] In the head-to-head comparison of sunitinib versus pazopanib, 27% and 14% of patients had stomatitis, 36% and 26% had dysgeusia, and 18% and 9% had epistaxis, respectively.[8] Overall, of patients treated with sunitinib and pazopanib, treatment was discontinued permanently because of adverse events in 20% and 24%.[15] In the Axis trial of axitinib versus sorafenib, 15% and 12% had stomatitis, 16% and 12% had mucosal inflammation, and 11% and 8% had dysgeusia, respectively.[16] The initial report of everolimus versus placebo showed stomatitis in as many as 40% of patients.[17] However, the comparison of everolimus and cabozantinib showed stomatitis in 24% and 22%, mucosal inflammation in 23% and 19%, and dysgeusia in 9% and 24%, respectively,[18] and the comparison of everolimus and nivolumab showed somatitis in 29% and 2%, mucosal inflammation in 19% and 3%, and dysgeusia in 13% and 3%, respectively.[4] The combination of everolimus and lenvatinib showed stomatitis in 29%, epistaxis in 18%, nasopharyngitis in 12%, oral pain in 12%, and mouth ulceration in 10%.[19] A recent study of IL-2/IFN versus IL-2/IFN/bevacizumab reported stomatitis in 17% and 32%.[20] Basically, all approved therapies for mRCC have the ability to cause mucosal irritation, stomatitis, and dysgeusia in a substantial number of patients. This might impair daily quality of life and might lead to dose reduction, discontinuation, or treatment shift. Moreover, the reporting of eye, nasal, pharyngeal, anal, or genital mucosal irritation is probably underestimated.[21] A recent meta-analysis of everolimus-induced mucositis in clinical trials comprising pancreatic neuroendocrine tumors, hormone receptor-positive/human epidermal growth factor receptor 2-negative breast cancer, mRCC, as well as tuberous sclerosis complex showed a stomatitis rate of 67%.[9] In essence, stomatitis represents a frequent and unpleasant toxicity.

To date, to our knowledge, no study to alleviate mucosal irritation has been reported, only supportive care means such as salt water or sodium bicarbonate oral rinses, sucking ice, use of soft toothbrush, steroids, and smoking cessation. Moreover, avoidance of hot, sour, salty, acidic, hard, and crunchy food, as well as avoidance of alcohol and agents that contain hydrogen peroxide are encouraged.[22] However, these restrictions are linked with poor daily quality of life for many patients and their families. To our knowledge, this study represents the first documentation of a specific therapy to alleviate mucosal toxicity. If mucosal adverse events can be reduced, patient daily quality of life will improve. Moreover, if overall treatment can be given without dose reduction, discontinuation, or shift in treatment, this might potentially improve treatment outcome. On the basis of comparable PFS and OS in our

Table 3 Univariate Cox Regression Analysis of PFS and OS of the Examined Cohort

Univariate Analysis	All Patients (n = 77)	Sunitinib-Treated Patients (n = 29)	Pazopanib-Treated Patients (n = 24)
CTCAE Mucositis Score (4, 3 vs. 2) in Relation to PFS	1.19 (0.69-2.04); $P = .538$	1.72 (0.66-4.48); $P = .266$	0.57 (0.16-2.04); $P = .389$
CTCAE Mucositis Score (4, 3 vs. 2) in Relation to OS	1.03 (0.59-1.80); $P = .906$	1.51 (0.56-4.10); $P = .416$	0.72 (0.24-2.21); $P = .568$

Subgroup analysis was not performed on groups with <20 patients.
Data are presented as HR (95% CI), except where otherwise noted.
Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events version 4.0; HR = hazard ratio; OS = overall survival; PFS = progression-free survival.

Table 4 Follow-up Data of the Examined Cohort

Survival and Progression	All Patients (n = 77)	Sunitinib-Treated Patients (n = 29)	Pazopanib-Treated Patients (n = 24)	Everolimus-Treated Patients (n = 10)	Other Treatments (n = 14)
Median Time to Death (OS), mo (Range)[a]	31 (1-114)	38 (4-114)	19 (1-48)	60 (18-107)	27 (5-110)
Median Time to Progression (PFS), mo (Range)[b]	14 (1-76)	22 (1-76)	15 (1-41)	15 (3-34)	8.5 (1-50)

Abbreviations: mRCC = metastatic renal cell carcinoma; OS = overall survival; PFS = progression-free survival.
[a]Measured from mRCC systemic treatment initiation.
[b]Measured for the relevant anticancer treatment during folic acid supplementation.

study, we found no reason to suspect that use of folic acid supplements adversely affected the effect of the anticancer therapy. A prospective evaluation of folic acid is ongoing: FASTERCC (Folic Acid Supplement vs. placebo for Treating mucositis adverse Events in metastatic Renal Cell Carcinoma patients receiving targeted therapy). A randomized, double-blind trial from the DAnish RENal CAncer group (DARENCA study-4; NCT03581773) is ongoing. The primary end point is the change in mean degree of CTCAE mucositis (nasal, oral, pharyngeal, anal, or genital) according to the Common Terminology Criteria for Adverse Events version 4.0.

Patients receiving methotrexate (MTX) for rheumatoid arthritis often experience mucositis, and rheumatologic patients benefit from folic acid supplementation during MTX treatment.[23] MTX is known to competitively inhibit DHFR. It is unknown whether targeted therapies and immunotherapies inhibit DHFR. The folic acid mechanism of action might be involved in improved mucosal cell repair by providing a crucial factor for DNA synthesis.

The interpretation of toxicity should be done with caution. Some "toxicity" reflects on-target effect and is correlated with favorable outcome and should therefore not be avoided but should be acknowledged and appropriately treated. This is the case with hypertension, neutropenia, thrombocytopenia, hand-foot syndrome,[24-27] hypothyroidism,[28] and pneumonitis.[29] However, the most common adverse events to TKI associated with daily poor quality of life are fatigue, loss of appetite, diarrhea, nausea, and mucositis. Neither fatigue nor mucositis have been associated with favorable outcome[9] and are thus only linked with poor quality of daily life.

Limitations to the present study are the retrospective nature without a systematic, prospective toxicity data collection, the low patient number, the various systemic treatments, the titration of folic acid, and the nonrandomized design. Furthermore, this study does not offer any control group, which makes it difficult to identify any decrease in toxicity on the basis of factors other than folic acid supplementation. During this study, however, registration of mucositis was a pronounced priority; therefore, the authors assume systematic data collection for the patients. Despite the limitations, all patients had severe toxicity (ie, at least Grade 2 mucositis) before folic acid supplementation, and a clinically meaningful and statistically significant reduction in mucositis after folic acid supplementation was noted for all treatments, justifying further research of the potential benefit of folic acid.

Conclusion

Folic acid supplementation significantly reduced mucositis to a level without constraints for patients with mRCC treated with contemporary systemic therapy. Because this was a retrospective study without a control group, a prospective, double-blind, placebo-controlled evaluation of the effect of folic acid supplementation in mRCC patients is ongoing (NCT03581773).

Clinical Practice Points

- Mucositis is a frequent side effect of targeted therapy in mRCC patients.
- Mucositis leads to dose reduction, discontinuation, or treatment shift.
- We found folic acid reduced mucositis in mRCC patients receiving systemic therapy.
- Patient outcomes were equal or better than expected.
- A double-blind, placebo-controlled prospective study is ongoing (NCT03581773).

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Disclosure

The authors have stated that they have no conflicts of interest.

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