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# Capecitabine for squamous cell carcinoma reduction in solid organ transplant recipients

Andrew D. Breithaupt, MD, David Beynet, MD, and Teresa Soriano, MD  
Los Angeles, California

**Key words:** capecitabine (Xeloda); chemoprevention; solid organ transplant; squamous cell carcinoma.

## INTRODUCTION

Immunosuppression associated with solid organ transplantation significantly increases the rate of nonmelanoma skin cancer (NMSC) development, in particular squamous cell carcinomas (SCCs). In certain cases, the rate at which these malignancies develop can be too rapid for traditional surgical or field treatments. In these cases, chemopreventative treatments should be considered to decrease the rate of NMSC development so that the remaining can be managed by more traditional treatments. Herein, we show that capecitabine can be used as a viable chemopreventative option for these difficult cases.

## CASE

We present the case of a 68-year-old white man who had bilateral lung transplantation for smoking-related chronic obstructive pulmonary disease on October 4, 2006 with excellent allograft function postoperatively. The patient's immunosuppressive medications were limited to prednisone 5 mg daily and sirolimus 1 mg daily. Before transplantation, the patient had no history of nonmelanoma skin cancers. Approximately 1 year after transplantation, he had his first skin cancer, an SCC. He continued to have numerous SCCs, especially on his scalp and hands, requiring multiple surgical resections and reconstructions. By the time of his death in 2013 he had had 98 SCCs.

Because of rapid increase in number and aggressive growth of his SCCs during his posttransplantation course, he started taking acitretin in June 2008, beginning at 10 mg and titrated up to 25 mg. This resulted in a modest but noticeable decrease in the rate of NMSC development. Despite being on acitretin, in 2009 he had a poorly differentiated SCC on his right dorsal hand. The SCC showed in-transit metastasis on punch biopsy of the ipsilateral forearm

### Abbreviations used:

5-FU:	5-fluorouracil
NMSC:	nonmelanoma skin cancer
SOTR:	solid organ transplant recipient
SCC:	squamous cell carcinoma

and had an involved ipsilateral axillary node. Acitretin was discontinued, and he was treated with chemotherapy consisting of 6 cycles of cisplatin and 5-fluorouracil. He had an excellent response to therapy with subsequent negative positron emission tomography/computed tomography surveillance.

In 2010, he continued to have SCCs on his head and neck. The patient started a skin cancer suppression regimen of capecitabine 1000 mg twice a day, 7 days on, 7 days off, for a total of 6 months. He tolerated the therapy well with minimal side effects and had a decreased incidence of cutaneous SCCs. In 2011, 6 months after completion of his course of capecitabine, he again had subsequent multiple SCCs; thus, he was given another regimen of capecitabine, increased to 1500 mg twice a day, 7 days on, 7 days off, for a total of 6 months but was ultimately stopped because of intolerance of side effects.

Because of capecitabine therapy, SCCs were developing at rate of approximately 18 per year. After initiating therapy in March of 2010, the rate decreased to 12 SCCs per year, a 33% reduction. After stopping this first course, the patient again began to have new lesions as noted by the small peak in 2011 (Fig 1). After this rebound, a second higher course of capecitabine led to a durable response to decrease his rate of SCC formation (Fig 1). This decrease lasted until in 2012, when he had a recurrence of the right dorsal hand metastatic SCC and was restarted on

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Correspondence to: Andrew D. Breithaupt, MD, 200 Med Plaza, Suite 465, Los Angeles, CA 90095. E-mail: [abreithaupt@gmail.com](mailto:abreithaupt@gmail.com).

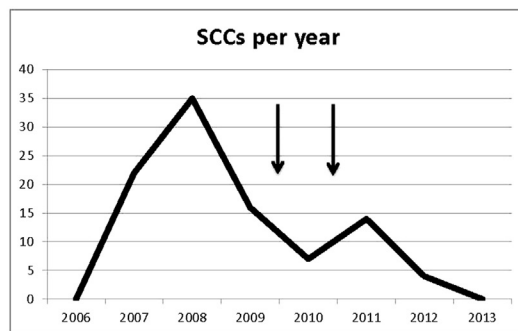
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SCCs per year	2006	2007	2008	2009	2010	2011	2012	2013
	0	22	35	16	7	14	4	0



**Fig 1.** SCCs diagnosed per year for the patient presented. The 2 arrows indicate the initiation of 2 separate courses of capecitabine treatment.

chemotherapy. He ultimately died in 2013 from acute myelogenous leukemia.

## DISCUSSION

Compared with the general population, solid organ transplant recipients (SOTRs) have a significantly higher incidence of nonmelanoma skin cancers.<sup>1</sup> This is because of immunosuppressive medication, with an increased degree of immunosuppression corresponding to an increased incidence of NMSC. Skin cancers in SOTRs also tend to behave more aggressively than in the general population and have a greater metastatic potential.<sup>2</sup> Therefore, skin cancer screening and prevention should be an integral part of any posttransplant regimen.

Although surgical and physical interventions like Mohs micrographic surgery and liquid nitrogen are frequently used to manage cancerous and precancerous lesions in SOTR, these lesions become a burden, at which point adjuvant therapy should be considered. Several adjuvant therapies exist to reduce the number of NMSCs including topical 5-fluorouracil (5-FU), topical imiquimod, topical and systemic retinoids, and photodynamic therapy.

Acitretin is a systemic retinoid used as adjuvant therapy in SOTRs for NMSC reduction and is often considered in patients with significant SCC burden, typically between 5 and 10 SCCs a year. Multiple studies have found that acitretin leads to a statistically significant reduction in SCCs in SOTRs with follow-up ranging from 6 months to 5 years.<sup>3</sup> A significant number of patients are unable to tolerate the side effects including severe xerosis, cheilitis, and dry eyes. Additionally, patients must be maintained on systemic retinoids to avoid a rebound effect that occurs if the medication is stopped, which can lead

to the rapid development of numerous and aggressive SCCs.

Capecitabine is a prodrug of 5'-deoxy-5-fluorouridine that is converted enzymatically to its active metabolite 5-FU. It was initially approved by the US Food and Drug Administration in 1998 for breast cancer and subsequently in 2001 and 2005 for metastatic and primary colon cancer, respectively. It was observed that in some breast cancer patients being treated with capecitabine, actinic keratoses became inflamed and some subsequently resolved.<sup>4</sup> This observation is similar to the effects of topically applied 5-FU.

Oral low-dose capecitabine has since been used in certain cases for chemoprevention of NMSC in SOTR.<sup>5</sup> It is typically administered at 0.5 to 1.5 g/m<sup>2</sup> daily for days 1 to 14 of a 21-day treatment cycle. Treatment cycles are repeated until disease progression or the development of intolerable toxicity. Studies have shown this regimen to induce a statistically significant reduction of both SCCs and actinic keratoses.

Although low-dose capecitabine is tolerated well by most patients, treatment-limiting side effects may be observed in up to 30% of patients.<sup>6</sup> The most commonly reported side effects include fatigue, diarrhea, hand-foot syndrome, neutropenic fever, and stomatitis.

Prior to initiating treatment, patients should be screened for dihydropyrimidine dehydrogenase deficiency.<sup>6</sup> If present, this may lead to severe capecitabine toxicity. Additionally, renal function should be assessed before treatment, as impaired function may contribute to the development of severe side effects.

In our case, capecitabine was used as adjuvant preventive therapy in a SOTR with a resultant significant decrease of his SCC disease burden. The

patient's initial response to chemotherapy for his metastatic disease was successfully maintained for 2 years with 2 separate regimens of capecitabine. Further studies are needed to help define the role that capecitabine plays in the prevention of NMSC in SOTRs. Future research may help improve the tolerability of the treatment and limit side effects. We suggest that for certain SOTR patients with significant NMSC burden that capecitabine offers a viable adjuvant therapy to help control disease.

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