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Elective Checkpoint Inhibitor Discontinuation in Metastatic Solid Tumor Patients: A Case Series

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Abstract

Introduction: Checkpoint inhibitor (CKI) therapy has markedly altered the survival of patients with many solid tumors. It appears clear that 10-40% of patients with a number of metastatic cancers can achieve lengthy remissions following CKI therapy. The optimal duration of treatment or whether treatment can ever be safely stopped is still controversial. Based on melanoma-derived data, we tested whether CKI treatment could safely be discontinued in patients with other solid tumors.

Methods: A retrospective analysis was performed in adults with metastatic solid tumors treated with CKI-based therapy. Patients with solid tumors who achieved complete remission on 2 sequential scans at least 3 months apart during ongoing treatment were identified from our computerized patient database. Patient data was analyzed for patient characteristics, as well as progression-free and overall survival.

Results: A total of 69 non-melanoma solid tumor patients were treated with CKI-based regimens in our clinic and 14 achieved complete remission (20.3%). Five patients were female (35.7%) and the remaining nine were male (64.3%). A 100% progression-free survival was observed for these patients. The median duration of complete remission was over 20 months from the time of elective treatment discontinuation. Median overall survival was not reached in this cohort. One patient died of non cancer-related causes.

Conclusions: Based on this retrospective case series, elective treatment discontinuation in patients who achieved complete remission appears feasible. All patients remained in a durable complete remission after treatment discontinuation. We hypothesize that appropriate selection of patients for early treatment discontinuation may decrease their economic burden related to ongoing treatment, limit potential toxicity, and improve quality of life.

Keywords: Kidney cancer; Skin cancer; Anal squamous carcinoma; Cervical cancer; Non-small cell lung cancer; Head and neck squamous cell carcinoma

Introduction

Cancer is a major public health concern worldwide and represents the second leading cause of overall mortality [1]. In the year 2021, 1,898,160 new invasive cancer diagnoses were estimated to have occurred in the United States, along with 608,570 cancer deaths [2]. Development of tumor metastases is known to be responsible for nearly 90% of all cancer deaths [3]. Fortunately, there have been important advances in cancer treatment in the last 30 years. Since 1991, the cancer death rate has decreased significantly due to improvements in detection and treatment [2]. The development of targeted therapies and immune checkpoint inhibitors (CKI) has been pivotal in improving survival of patients with metastatic cancer [4,5]. Patients receiving targeted therapy generally require continuous treatment. It has become clear that a percentage (10-40%) of patients treated with CKI based immunotherapy for metastatic solid tumors will achieve complete remission and may benefit from long-term survival. It is not clear what the optimal duration of CKI therapy should be following remission or whether treatment can ever be safely stopped. A prolonged duration of CKI therapy is likely to increase medical costs, decrease patient quality of life, and potentially increase the risk of immunologic toxicity. There is currently no generally accepted strategy for discontinuation of CKI treatment in responding patients with solid tumors. In many previous studies, patients who were benefiting from treatment without undue toxicity were continued on treatment indefinitely or for an arbitrary length of time (e.g., 1 or 2 years)(reviewed in [6,7]. In studies of pembrolizumab monotherapy in metastatic melanoma, Robert et al. proposed a strategy for treatment discontinuation for patients who achieved complete response [8]. These investigators found a low rate of relapse (~10%) in patients who discontinued treatment once patients achieved documented complete remission on 2 sequential scans, at least 3 months apart [9]. Based on an extensive experience with elective treatment discontinuation in our own melanoma patients (Perez L, Samlowski W, Lopez- Flores R, manuscript in press Biomedicines, 2022), we have employed a similar treatment discontinuation strategy in patients with other metastatic solid tumors. We describe the successful clinical application of this treatment discontinuation paradigm in a small sequential series of solid tumor patients.

Materials and Methods

Patient population

This retrospective case series consists of adult patients with metastatic solid tumors treated with CKI-based therapy, CKI plus targeted agents, or CKI plus chemotherapy by a single community oncologist (WS). The goal was to evaluate the potential outcome of an accelerated treatment discontinuation strategy in patients with a radiologic or pathologically defined complete response. Eligible patients were identified via a search of the iKnowMed medical record database (McKesson, Inc) to identify patients treated with PD-1- or PD-L1- directed monoclonal antibodies pembrolizumab, cemiplimab, nivolumab or avelumab. These patient records were reviewed, and deidentified patient data was extracted into a password-protected spreadsheet. Extracted data included: age, gender, race or ethnicity, comorbid conditions, treatment regimens, number of doses of CKI, date of treatment start and end, duration of CKI treatment, lymphocyte/neutrophil ratio at the start of therapy, and best objective response. Treatment related toxicity was graded based on CTCAE 4.0 [10], and the cause of death (if applicable) was also extracted from the record. Patients who did not achieve complete response, who died during their initial treatment, or who had not discontinued treatment at the time of analysis were excluded. Patients who discontinued CKI therapy due to toxicity were also excluded. This retrospective analysis of existing clinical data was reviewed by the Western IRB chair and deemed exempt from full IRB review.

Patient treatment

CKI therapy regimens have evolved over the period of this study. Thus, patients were treated with nivolumab (either 3 mg/kg or fixed dose 240mg every 2 weeks or 480 mg every 4 weeks), pembrolizumab (2mg/kg or 200 mg fixed dose every 3 weeks), avelumab (10 mg/kg every 3 weeks), or cemiplimab (350 mg fixed dose every 3 weeks). Two patients were treated with a modified schedule of ipilimumab (1 mg/kg every 3 weeks) plus nivolumab (3 mg/kg every three weeks), followed by fixed dose nivolumab maintenance [10]. Patients were evaluated for toxicity prior to each treatment by clinical examination and standard laboratory testing (including endocrinopathy screening). Only patients who achieved a radiologic or clinically determined complete response were considered for elective treatment discontinuation. These patients continued CKI therapy for three additional months until a follow-up scan or clinical exam confirmed the complete remission. At this point, elective treatment discontinuation was considered. One patient required a biopsy of persistent lesions to verify a pathologic complete response.

Statistical Analysis

Patient information was recorded in a deidentified manner into a password-protected Excel spreadsheet (Microsoft, Redmond WA) for analysis and calculation of descriptive statistics (maximum, minimum values, median, and standard deviation). Progression-free and overall survival were evaluated via Kaplan-Meier analysis [11].

Results

A total of 69 patients received CKI treatment for metastatic solid tumors. Fourteen of these patients achieved complete remission (20.3%) and underwent planned treatment discontinuation as described. Patient characteristics are shown (Table 1). Of the patients who achieved complete remission, five were female (35.7%) and the remaining nine were male (64.3%) (Table 1). Among these patients, twelve identified as Caucasian, one as African American, and two as Hispanic. The median age was 67.5±15.6 years (±SD). Six patients had non-small cell lung cancer (NSCLC), four had cutaneous squamous cell carcinoma (CSCC), one had clear cell renal carcinoma (ccRCC), one had anal squamous cell carcinoma, one had cervical adenocarcinoma, and one had squamous cell carcinoma of the head and neck (SCCHN) (Table 1). All patients had stage IV disease at the initiation of treatment. Patient comorbidities are described (Table 1). The median number of CKI doses was 17.5 with an average of 17.1±10.2. The minimum number of doses administered was 5 while the maximum was 36 (Table 2). Eleven patients achieved a radiologic complete response (80%) while two patients had residual small lesions that were too small to biopsy (20%). One patient required a biopsy of a residual stable pancreatic lesion to verify a pathologic complete response (Table 2). None of the patients who achieved complete response and underwent planned treatment discontinuation have relapsed (100% PFS), with over 20 months median follow-up from the end of treatment. Median overall survival (OS) from the start of therapy has not been reached, with over 88% overall survival in patients with over 20 months from the start of therapy (Figure 1). One patient (Patient 3) died of COPD-associated pneumonia and not of his underlying NSCLC, which remained in remission at the time of death. To date, all patients except for one have spent less time undergoing treatment (orange) than the time spent in unmaintained complete remission after treatment discontinuation (blue) (Figure 2).

UPN	Age	Sex	Race-Ethnicity	Cancer	Histology	Stage	Comorbid conditions
1	38	F	H	RCC	clear cell	IV	
2	53	F	C	anal	SCC	IV	Macrocytosis, lung nodule, HTN, benign paroxysmal positional vertigo, nicotine dependance (cigarettes), leukopenia, hypoxia
3	60	M	H	NSCLC	adenocarcinoma	IV	Arthritis, COPD
4	42	F	C	cervix	adenocarcinoma	IV	Anxiety disorder, night sweats, anemia, dehydration, rash, leg pain/ swelling, postphlebitic syndrome with inflammation
5	74	F	C	NSCLC	SCC	IV	Myeloproliferative disease (chronic), COPD, splenomegaly, esophageal dysphagia, hypothyroidism
6	68	F	C	NSCLC	adenocarcinoma	IV	tobacco use, low back pain, HTN, arthritis, and GERD
7	60	F	C	NSCLC	adenocarcinoma	IV	Bleeding tendency, bronchitis, HTN, paroxysmal atrial fibrillation, COPD, anxiety, dehydration
8	84	F	C	NSCLC	adenocarcinoma	IV	Bronchitis, hypothyroidism
9	91	M	C	skin	SCC	IV	Prostate cancer, pacemaker, diabetes, HTN, CAD, GERD, Hypercholesterolemia, Sinus bradycardia
10	72	M	C	skin	SCC	IV	Monoclonal gammopathy, BPH, CLL
11	67	F	C	skin	SCC	IV	Anxiety, hypercholesterolemia, chronic pain syndrome
12	71	M	C	skin	SCC	IV	Hypothyroidism, UC, enterocolitis, HTN, dry mouth, hyperglycemia, hypercholesterolemia, prostate CA
13	59	M	AA	SCCHN	SCC	IV	Hypercholesterolemia, ankylosing spondylitis, anxiety disorder
14	64	F	C	NSCLC	adenocarcinoma	IV	Papillary thyroid cancer, liver disease, acoustic neuroma syndrome, neuropathic pain, pulmonary embolism

UPN, unique patient number; F, female; M, male; C, Caucasian; H, Hispanic; AA, African-American; RCC, renal cell carcinoma; NSCLC, non-small cell lung cancer; SCCHN, squamous cell carcinoma of the head and neck; SCC, squamous cell carcinoma; HTN, hypertension; COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; CAD, coronary artery disease; BPH, benign prostatic hyperplasia; CLL, chronic lymphocytic leukemia; UC, ulcerative colitis.

Table 1: Patient demographics.

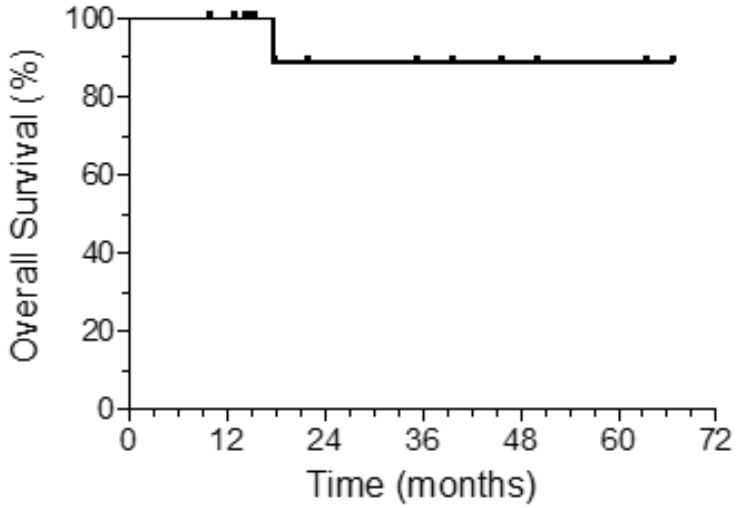

Figure 1: Overall survival of patients who electively discontinued CKI therapy.

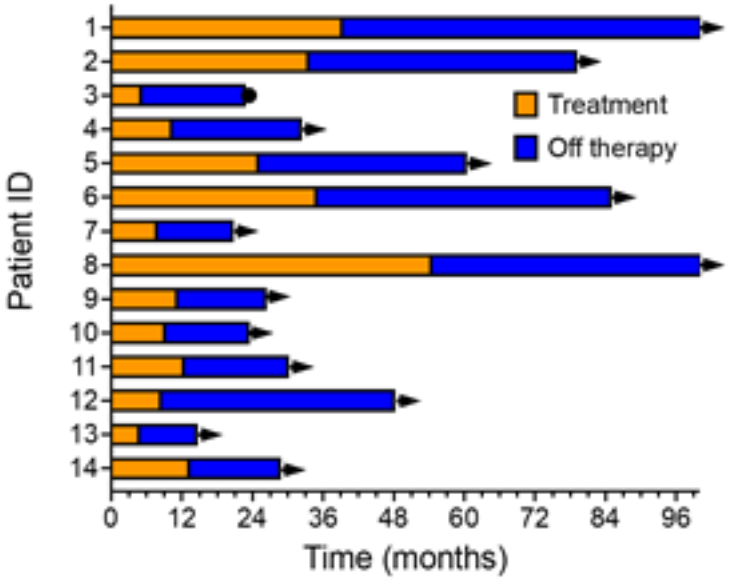

Figure 2: Swim-lane plot demonstrating time receiving CKI-based therapy (orange) versus time in unmaintained remission after elective treatment discontinuation. Arrows indicate ongoing remission, while a dot at the end of the line indicates a patient death.

The acute toxicity reactions were typical of CKI therapy and included G1-2 diarrhea, edema, anasarca, arrhythmia, tachycardia, pleural effusion, and hypothyroidism (Table 2). Patient two had acute diarrhea and C. difficile that were resolved with steroids and oral vancomycin. Patient three had hand and foot edema that resolved, but chronic problems with anasarca and pleural effusions.

Patient five developed urinary tract sepsis and was admitted to the hospital for two weeks but has since recovered and had no other toxicity. Patient six had acute shortness of breath, diarrhea, and abdominal pain for which treatment was held for a month allowing for full recovery. Patient seven had acute supraventricular arrythmia and chronic pleural effusions, which have persisted. Patient eight developed hypothyroidism, mildly elevated transaminases, and a faint pruritic rash for which treatment was delayed for one month, allowing for full resolution of symptoms and treatment continuation. Patient thirteen had diarrhea from sunitinib which resolved after 1 week of steroid therapy. Patient fourteen developed pulmonary necrotizing granulomas, which improved with treatment. No treatment-related toxicity was experienced by 7 patients.

UPN	CKI agent	Dosage	CKI doses	added TT or chemotherapy	OR	PFS (months) from EOT	OS (months)	CKI toxicity
1	N	3mg/kg q2w	36	everolimus	PR-a	39.4	63.3	–
2	N	240mg q2w	22		PR-a	33.6	45.6	diarrhea + c. diff
3	P	200 mg q3w	18	pemetrexed	CR	5.3	17.6	hand foot edema, anasarca
4	P	200 mg q3w	17		CR	10.4	22.0	–
5	N	240mg q2w	14	carboplatin/paclitaxel/ RT	CR	25.2	35.2	UTI
6	P	200 mg q3w	20		CR	35.1	50.0	SOB, diarrhea, abd pain
7	P	200 mg q3w	6	pemetrexed	CR	7.9	12.9	arrythmia, pleural effusion
8	A	10mg/kg q3w	26		CR	54.6	66.6	hypothyroidism
9	C	350mg q3w	5		CR	11.4	15.0	–
10	C	350mg q3w	8		CR	9.3	14.2	–
11	C	350mg q3w	8		CR	12.5	17.7	–
12	I/N	1mg/kg+3mg/kg,	35	sunitinib	CR	8.6	39.7	–
13	N	480mg q4w	6		CR	4.9	9.8	–
14	I/N	1mg/kg+3mg/kg	19	pemetrexed	CR-bx	13.4	15.4	necrotizing granulomas-lung

UPN, unique patient number; CKI, checkpoint inhibitor; N, nivolumab; P, pembrolizumab; A, avelumab; C, cemiplimab; I, ipilimumab; OR, objective response; PR, partial response; PR-a, partial response but lesions too small to biopsy; CR, complete response; CR-bx, CR proven by biopsy; PFS, progression-free survival; OS, overall survival; UTI, urinary tract infection; c. diff, clostridium difficile; SOB, shortness of breath; abd, abdomen

Table 2: Treatment and outcome.

Discussion

CKI treatment has dramatically changed the management of many solid tumors (e.g., non-small cell lung and renal cancer). A small but increasing percentage of solid tumor patients, ranging from 10-40%, achieve complete remission (CR) following CKI therapy [12-16]. It is likely that additional combinations of CKI, or chemotherapy or targeted therapy added to CKI treatment, will further improve outcomes, with increasing numbers of patients achieving complete remission in a variety of solid tumors [17]. Due to variability in prior clinical trial designs, it is not currently known how long responding patients need to continue therapy after achieving complete remission (CR) to maintain an ongoing response. Thus, the optimal duration of treatment, or whether treatment can ever be safely stopped once remission is obtained remains uncertain. At present, most of the data related to treatment discontinuation has been derived from melanoma patients. These studies have suggested that elective treatment discontinuation is feasible and relatively safe in patients who have achieved a confirmed complete response. In our own metastatic melanoma patient series, over 92% of patients who

achieved a CR remained in long-term remission once treatment was electively discontinued (L. Perez, W. Samlowski, and R. Lopez-Flores, in press Biomedicines, 2022). With 26-month median follow-up, progression-free survival was 97.5% at 1-year and 94% at 3-years. Four of the 46 individuals with complete remission (8.7%) eventually relapsed at a median of 27 months after treatment discontinuation. Using a similar elective treatment discontinuation approach, Robert et al. have also observed a relapse rate of approximately 10% in a subset of pembrolizumab treated melanoma patients who electively discontinued therapy in the Keynote 001 trial [18].

There are limited clinical trials that have attempted to evaluate the optimal CKI treatment duration in solid tumors. In NSCLC, a randomized trial was performed with randomized PD-1 antibody discontinuation at 1 year versus 2 years of therapy. This trial suggested a benefit for ongoing therapy beyond 1 year [12]. It should be noted that this study randomized not only patients who achieved a complete response to early treatment discontinuation, but also patients with partial response, stable disease, or even gradual progression who were felt by investigators to be benefitting from therapy [19]. Based on our own experience, we electively discontinued CKI therapy in patients with solid tumors, who achieved a stable CR on two sequential scans three months apart during continued CKI treatment. Our study included patients treated with a variety of different immunotherapy regimens, and in some cases patients who achieved complete response with targeted therapy added to CKI treatment. Fourteen patients (20.3%) achieved complete response. None of these patients have relapsed after treatment discontinuation with a median of over 20 months follow-up. It is important that elective treatment discontinuation should only be considered for patients who had achieved a radiologic or pathologically confirmed complete response. This observation is supported by a multivariate analysis of patients discontinuing therapy in 5 German treatment centers [20]. These investigators found that discontinuation of therapy in patients with partial remission or stable disease was associated with a significant decrease in progression-free survival compared with patients who were in complete remission [20]. A shorter treatment duration is advantageous for a variety of reasons. Shorter duration of CKI exposure has the potential to decrease the risk of treatment-related adverse events [21]. Once treatment is discontinued, toxicities become easier to manage and frequently subside. A shorter duration of therapy is also likely to decrease the economic burden of treatment. Average treatment cost for single agent PD-1 therapy frequently exceed $10,000 per month in the United States [22], while combination CKI therapy or addition of targeted agents to CKI treatment result in a marked escalation of drug costs. Drug costs appear to account for 80-85% of the total treatment costs for CKI therapy [23,24]. With previous standards of treatment duration lasting 2 years or more, the economic burden on patients and payors is substantial. It is likely that decreasing treatment duration in appropriate patients could result in appreciable cost saving. Moreover, treatment of CKI-induced toxicity adds substantial additional medical care costs [25]. If treatment duration is reduced, it is likely that patient quality of life will also improve. Frequent office visits, labs, and scans result in considerable time constraints and stress that negatively affects patient quality of life. Appropriate consideration of early treatment discontinuation allows patients to return to their usual daily activities and normal employment sooner.

Conclusion

There is currently little data about CKI discontinuation in non-melanoma patients who achieve a confirmed complete remission. In our experience, these patients have a relatively low risk of disease recurrence when CKI treatment is electively discontinued. We suspect that with the expansion of patient numbers, a small percentage of patients will undergo eventual disease progression, based on our experience in melanoma patients. It remains to be seen if retreatment with CKI can be utilized to salvage the infrequent patients who relapse after treatment discontinuation. It is clear that further work is needed to improve complete response rates to encompass a higher percentage of patients.

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