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ORIGINAL ARTICLE

Quality-of-life evaluation during platinum-based neoadjuvant chemotherapies for urothelial carcinoma

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Abstract

Background Although quality of life (QOL) is one of the most important considerations in patients treated with anticancer therapies, desirable regimens for neoadjuvant chemotherapy including QOL in locally advanced urothelial carcinoma remain unclear. The present study evaluated the influence of neoadjuvant platinum-based chemotherapy on QOL in patients with locally advanced urothelial carcinoma.

Methods Between June 2013 and March 2016, 83 urothelial carcinoma patients who received two courses of neoadjuvant chemotherapy were enrolled in this prospective observational study. Neoadjuvant regimens included gemcitabine + cisplatin (GCis) or gemcitabine + carboplatin (GCb) therapies. As a primary endpoint, we assessed QOL changes in each group before and after chemotherapy using the Quality of Life questionnaire on days 1, 3, and 15 of each cycle. Secondary endpoints included toxicity, safety, weight loss, renal function decline, and tumor responses.

Results QOL analyses were performed in 39 patients receiving GCis and in 44 patients receiving GCb. Appetite loss, role functioning, nausea/vomiting, physical, and fatigue deteriorated >10% from baseline in the GCis group but not in the GCb group. Constipation worsened, whereas scores for pain and emotional items improved in both groups. Objective response rates were 38.5 and 43.2% in the GCis and GCb groups, respectively.

Conclusions Both GCis and GCb regimens were feasible in terms of QOL. The GCb regimen may be associated with

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a better QOL status especially in regard to gastrointestinal symptoms.

Introduction

In recent years, reflecting an increased focus on a patient-centered view, the interest in patient-reported outcomes to treatment-related toxicity has gained increasing prominence [1, 2]. Enhancing quality of life (QOL) as a goal for anticancer therapeutics is becoming a major factor in therapeutic decision making in advanced or metastatic disease. QOL is also important in patients who undergo neoadjuvant chemotherapy, considering that choosing an effective anticancer therapy with minimal toxicity is desirable before implementing definitive therapy. However, limited evidence of QOL during neoadjuvant therapy for locally advanced urothelial carcinoma (UC) is available [3, 4].

Current guidelines recommend cisplatin-based neoadjuvant chemotherapy for patients with locally advanced UC [5]. Although cisplatin-based chemotherapy is effective, ~40% patients are ineligible because of nephrotoxicity [6, 7], and non-cisplatin-based regimens are used as alternatives. Among these, carboplatin-based regimens are reportedly efficacious in the treatment of patients with renal impairment [3, 7–9] or clinical T2 disease [10]. In addition, our previous study suggested that a gemcitabine + carboplatin (GCb) regimen with low toxicity facilitated completion of neoadjuvant therapy without dose reduction, prevented the delay in radical cystectomy, and resulted in a favorable oncological outcome [7]. However, there are currently no data supporting carboplatin-based regimens for UC patients who are unsuitable for neoadjuvant cisplatin treatment. Because few studies exist on this topic [3, 4], ideal regimens for neoadjuvant chemotherapy including QOL in locally advanced UC remain unclear.

In the present study, we prospectively evaluated QOL before and after neoadjuvant chemotherapy, including gemcitabine + cisplatin (GCis) or GCb in patients with locally advanced UC. This study was registered as a clinical trial (UMIN000020784).

Patients and methods

Ethics statement

This study was performed in accordance with the ethical standards of the Declaration of Helsinki and was approved by the ethics review board of the Hirosaki University School of Medicine (Authorization Number 2013-075). All participants provided written informed consent.

Patient selection and systemic chemotherapy

Between June 2013 and December 2016, we enrolled 83 patients with locally advanced UC who received two courses of neoadjuvant chemotherapy (GCis or GCb) in our hospital. Regimens were selected on the basis of guidelines regarding eligibility for proper use of cisplatin [11]. All patients received chemotherapy upon hospitalization. Patients received either GCis (800 mg/m^2 gemcitabine on days 1, 8, and 15 plus 70 mg/m^2 cisplatin on day 2 every 21 days, or GCb (800 mg/m^2 gemcitabine on days 1, 8, and 15 along with carboplatin at an area under the curve of 4, according to the Calvert formula, on day 2 every 3 weeks) for two cycles [9, 10]. Oral antiemetic (aprepitant) was administered for 3 days with a 5-HT3 receptor antagonist and dexamethasone to patients receiving GCis as antiemetic prophylaxis, according to the guidelines of the American Society of Clinical Oncology. Oral aprepitant was not used in the GCb group. Relative dose intensity was evaluated for each patient, and expressed as percentages.

Variable evaluations

The variables of age, gender, body mass index, Eastern Cooperative Oncology Group performance status (ECOG-PS), comorbidities (history of cardiovascular disease, or type-2 diabetes), regimen of chemotherapy, clinical stage, and renal function were recorded for all subjects. Renal function was assessed according to estimated glomerular filtration rates (eGFR) using a modified version of the abbreviated Modification of Diet in Renal Disease Study formula for Japanese patients [12].

QOL evaluations

We prospectively evaluated patient-reported QOL using the European Organization for the Research and Treatment of Cancer Quality-of-Life Questionnaire C30 (QLQ-C30) on days 1, 3, and 15 of each cycle. Patients with incomplete QLQ-C30 questionnaires at least before treatment (day 1 in first-course) were not eligible. The questionnaire includes five functioning scales (physical, social, role, cognitive, and emotional functioning), a scale for global QOL, and nine symptom scales (fatigue, pain, nausea/vomiting, dyspnea, appetite loss, sleep disturbance, constipation, diarrhea, and financial difficulties). Hematological (white blood cells, neutrophils, platelet cell counts, and anemia) and symptomatic (appetite loss, nausea/vomiting, and skin-related adverse events) toxicities were prospectively recorded according to the National Cancer Institute Common

Table 1 Patient backgrounds

	GCis	GCb	P value
n	39	44	
Age, years (IQR)	67 (62–73)	75 (69–80)	<0.001
Male, n	35 (90%)	30 (68%)	0.031
ECOG-PS (IQR)	0 (0–0)	0 (0–0)	0.445
Body mass index (IQR)	23.4 (21.9–25.8)	23.5 (21.2–24.8)	0.275
Type 2 diabetes, n	9 (23%)	5 (11%)	0.240
Cardiovascular disease, n	4 (10%)	7 (16%)	0.529
eGFR (IQR)	75 (67–84)	52 (39–61)	<0.001
Tumor location, n			
Bladder carcinoma (BC)	30 (77%)	25 (57%)	0.194
Upper tract urothelial carcinoma (UTUC)	8 (21%)	16 (36%)	
Both BC and UTUC	1 (2%)	2 (4.6%)	
Urethral carcinoma	0	1 (2.3%)	
Definitive therapy, n			
Radical cystectomy	28 (71%)	18 (41%)	0.012
Radical nephroureterectomy	7 (18%)	13 (30%)	
Radiotherapy	3 (7.7%)	12 (27%)	
Refused	1 (2.6%)	1 (2.3%)	

IQR interquartile range, *ECOG-PS* Eastern Cooperative Oncology Group performance status

Terminology Criteria for Adverse Events (CTCAE) version 4.0. QLQ-C30 scores, toxicity and safety, weight loss, and changes in renal function were compared before and after chemotherapy in each group. Tumor responses were analyzed according to the response evaluation criteria in solid tumors (RECIST) version 1.1.

Statistical analysis

Statistical analyses of clinical data were performed using SPSS version 22.0 (SPSS, Inc., Chicago, IL, USA) and GraphPad Prism 5.03 (GraphPad Software, San Diego, CA, USA). Categorical variables were compared using the Fisher's exact test or the chi-squared test. Quantitative variables were expressed as means ± standard deviations (SDs) or medians with interquartile ranges (IQRs). Differences between groups were compared using t test for normally distributed data or Mann–Whitney U test for non-normally distributed data, and differences were considered significant at $P < 0.05$. QOL differences before and after chemotherapy in each group were compared using the paired t test.

Results

Eighty-three patients who received neoadjuvant chemotherapy for localized disease were included in our QOL analysis. The numbers analyzed on QOL for each point (days 1, 3, and 15 in the first course and days 1, 3, and 15

in the second course) were 83/83 (100%), 80/83 (96%), 78/83 (94%), 78/83 (94%), 74/83 (89%), and 80/83 (96%), respectively. Because of cisplatin eligibility criteria, median age, male predominance, and eGFR levels were significantly greater, less, and lower in the GCb group than in the GCb group, respectively. Tumor location and median relative dose intensities did not differ significantly between
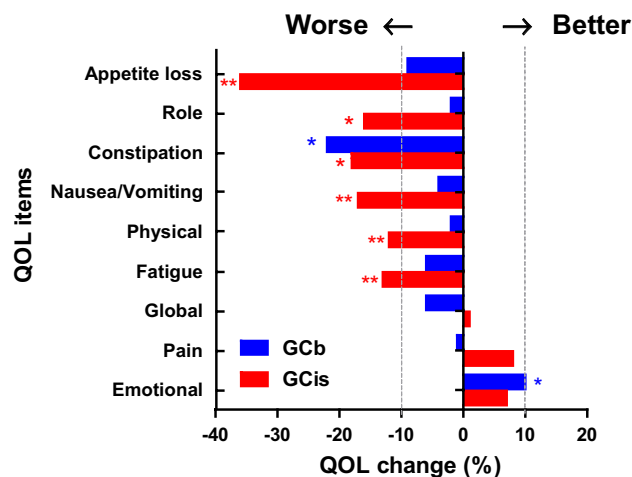

Fig. 1 QOL changes during two courses of chemotherapy. QOL items were assessed before and after chemotherapy for each group. Gastrointestinal symptoms, role functioning, physical, and fatigue showed a deterioration >10% in the GCis group. Appetite loss in the GCis group was the most affected symptom. Pain and emotional items showed improvements in both groups: *$P < 0.05$, **$P < 0.01$ compared with before chemotherapy (paired t test)

groups. However, significant differences between groups were observed in the distribution of definitive therapies (surgery or radiotherapy; Table 1).

The more relevant changes in QOL parameters reported after chemotherapy for each group are shown in Fig. 1. Because of baseline background differences between the GCis and GCb groups, QOL differences were compared between before and after chemotherapy in each group. Appetite loss, role functioning, nausea/vomiting, physical, and fatigue showed a deterioration >10% in the GCis group but not in the GCb group. Similarly, constipation worsened, whereas pain and emotional items improved in both groups. Other items in the QLQ-C30 showed no significant differences before and after chemotherapy. Figure 2 shows QOL trends during chemotherapy. In the GCis group, appetite loss (Fig. 2a), role functioning (Fig. 2b), nausea/vomiting

(Fig. 2d), and physical QOL scores became worse compared with baseline values. Constipation scores worsened soon after initiation of chemotherapy in both groups (Fig. 2c). However, scores for pain and emotional items were improved in both groups (Fig. 2f, g). Fatigue improved slightly in both groups at the beginning, but deteriorated in the GCis group by >10% by the end of treatment (Fig. 2h). Global QOL (Fig. 2i) after chemotherapy did not change in either group. A detailed comparison of QOL scores is shown in Table S1.

Hematological and symptomatic adverse events were evaluated using the CTCAE version 4.0 (Table 2). Major hematological and symptomatic adverse events in both groups were leucopenia/neutropenia and constipation. Between 54 and 59% of patients experienced appetite loss or nausea/vomiting in the GCis group, compared with only approximately 25% in the GCb group.
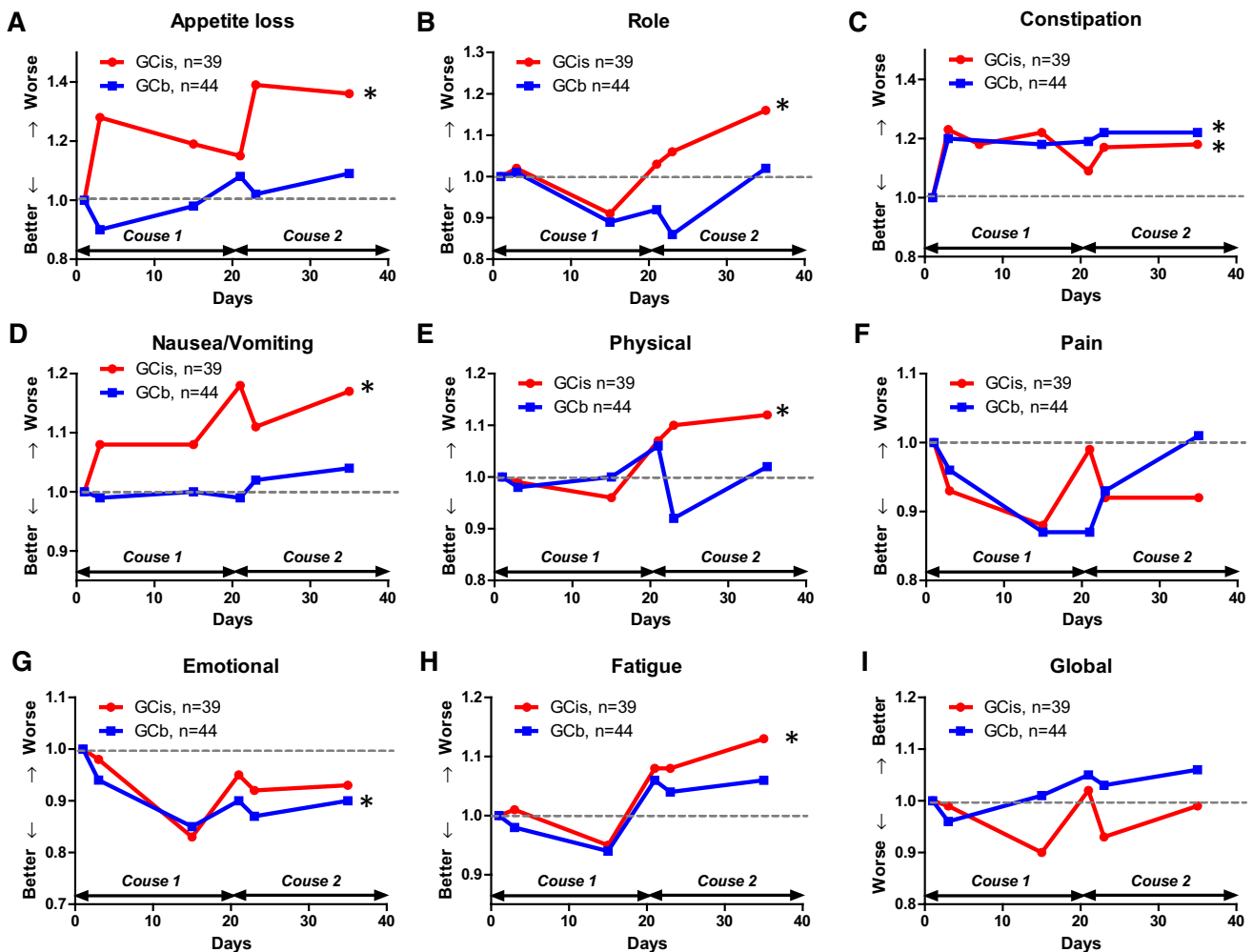

Fig. 2 QOL trends during chemotherapy. In the GCis group, appetite loss (**a**), role functioning (**b**), nausea/vomiting (**d**), and physical (**e**) QOL scores became worse compared with baseline. Constipation scores worsened soon after initiation of chemotherapy in both groups (**c**). However, scores for pain and emotional items were improved in

both groups (**f, g**). Fatigue improved slightly in both groups at the beginning, but deteriorated in the GCis group by >10% by the end of treatment (**h**). Global QOL (**i**) as compared with baseline did not change in either group. *Statistical significances (*P* < 0.05) between before and after chemotherapy in each group

Table 2 Chemotherapy-related adverse events and grades

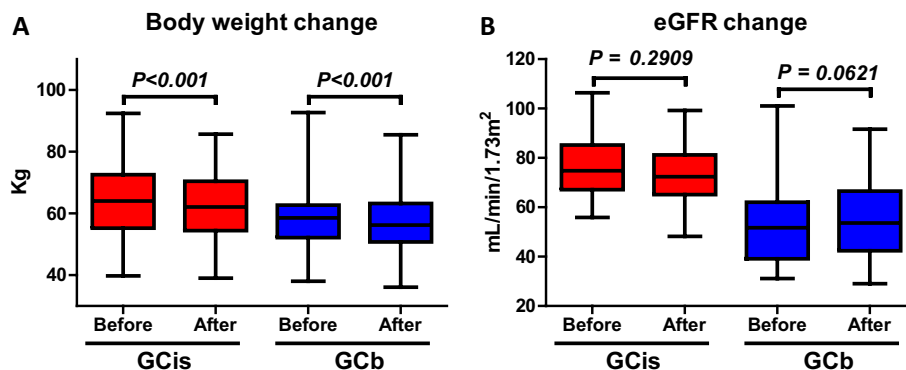| Hematological	GCis		GCb	
	All (%)	G3 (%)	All (%)	G3 (%)
White blood cells	97	72	93	50
Neutrophils	97	85	93	68
Platelets	95	21	86	20
Anemia	82	15	84	18
Increased creatinine	8	0	19	2
Symptomatic	GCis		GCb	
	All (%)	G3 (%)	All (%)	G4 (%)
Appetite loss	59	3	27	2
Nausea/vomiting	54	0	25	0
Skin	15	0	25	0
Diarrhea	8	0	2	0
Constipation	72	0	59	0
Febrile neutropenia		13		16

Fig. 3 Body weight and renal function changes during chemotherapy. Body weight was significantly and similarly decreased (median −2.5%, $P = 0.001$) in both GCis and GCb groups compared with the respective baselines (**a**). Although eGFR did not differ significantly in the GCis group (median 0%, $P = 0.2909$), it showed a marginally significant change in the GCb group (median 6.3%, $P = 0.0621$; **b**). *$P < 0.05$, **$P < 0.01$ compared with before chemotherapy (paired t test)

Changes in body weight and eGFR are presented in Fig. 3. Body weight significantly declined by 2.5% ($P = 0.001$) in both groups (Fig. 3a). In contrast, renal function did not change significantly in either group (Fig. 3b).

Measurable tumor responses were obtained in 66 patients. Median radiological tumor responses were 39.0 and 26.4%, and objective response rates were 38.5 and 43.2% in the GCis and GCb groups, respectively (Fig. 4).

Discussion

Patient-reported outcomes, including QOL, play important roles in the assessment of anticancer treatments. Although several studies evaluated QOL during chemotherapy in advanced UC patients receiving second-line or third-line therapy [13–15], only a few have evaluated QOL in UC patients receiving neoadjuvant chemotherapy [3, 4]. Therefore, we evaluated the impact of GCis or GCb regimens in terms of patient-reported QOL during neoadjuvant chemotherapy for locally advanced UC.

The essential findings of the present study are that GCis is associated with higher losses of QOL, especially in terms of gastrointestinal symptoms, role functioning, physical, and fatigue. These conclusions are summarized in Fig. 2, which shows longitudinal evaluations of QOL changes during chemotherapy, and suggests appropriate timing of prophylaxis. Whereas most QOL items showed a similar trend during both chemotherapies, appetite loss and nausea/vomiting
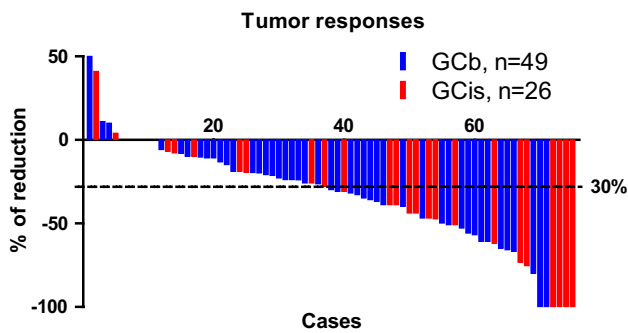
Fig. 4 Tumor responses. Although a comparison between groups was not statistically feasible in the present study, no significant differences in median tumor responses [GCis: 33%; GCb: 26%; ($P = 0.444$)] were found in patients with measurable tumors. Objective response rates (complete or partial response) were 15/26 (58%) and 22/49 (45%) for the GCis and the GCb groups, respectively, and did not differ significantly from each other ($P = 0.469$, chi-squared test)

increased notably by day 3 in the GCis group. Therefore, even though we used guideline-recommended prophylactic agents, the use of cisplatin on day 3 at each cycle seemed to clearly affect those symptoms. Constipation showed a similar tendency in both groups, and worsened soon after initiation of chemotherapy. This result suggests that prophylaxis for constipation should be started earlier. QOL items within the emotional functioning scale improved soon after initiation of therapies in both groups, which might be because of the comforting feeling of being treated. Fatigue symptoms showed a similar trend during treatments in both groups, and progressively worsened over time. Surprisingly, fatigue symptoms in the GCis group did not increase soon after initiation of therapy despite the presence of meaningful gastrointestinal symptoms. This result might suggest that fatigue itself is a separate symptom from appetite loss or nausea/vomiting. Global QOL scores for each group suggested that both neoadjuvant therapies were feasible, in terms of QOL, for patients with locally advanced UC. In addition, no significant differences in hematological toxicity or body weight loss were identified between GCis and GCb groups, despite significant age and sex differences at baseline. This may suggest the feasibility of GCb in terms of improving QOL in cisplatin-ineligible patients; however, our study design prevents analyzing statistical differences between GCis and GCb regimens due to the selection bias.

The use of carboplatin in the neoadjuvant setting is controversial [3, 7, 8, 10, 16], and the oncological efficacy of GCb remains unclear. A previous phase II study comparing GCis and GCb as first-line chemotherapies in metastatic UC patients reported objective responses (49.1 vs 40.0%) and median overall survival times (12.8 vs 9.8 months) that were not significantly different, but suggested comparatively favorable outcomes for the cisplatin-based regimen [3].

However, no clear evidence currently supports the superiority of cisplatin-based regimens over carboplatin-based regimens in the neoadjuvant setting [8, 17]. Accordingly, we designed a strategy involving neoadjuvant GCb chemotherapy followed by immediate surgery, and performed the present prospective single-arm study [7, 10]. The present study shows no clear differences in tumor responses, despite the presence of significant age and sex differences, and suggests that both GCis and GCb chemotherapy combinations have identical antitumor effects. Although the oncological outcomes were not endpoints in our study, we assessed progression-free and overall survival times (Fig S1). Before background adjustment, progression-free survival was significantly poorer in the GCb group (Fig S1A). However, the background (age, sex, renal function, tumor location, and ECOG-PS) adjustment model showed that selection of definitive therapy, rather than chemotherapy regimen, had a significant influence on progression-free intervals (Fig. S1B). Similarly, there were no significant differences between chemotherapy regimens in overall survival in Kaplan–Meier (Fig. S1C) and multivariate analyses (Fig. S1D); however, radiotherapy was selected as an independent risk factor for poor prognosis. Although the present study has clear limitations in terms of outcome analyses, our data indicate potential activity of GCb and suggest its plausibility as an option for patients with locally advanced UC who are unfit for neoadjuvant cisplatin.

Limitations of the present study include its small sample size, single-institution data, and the non-randomized design. The small sample size prevents definitive conclusions for the influence of chemotherapy on QOL in the neoadjuvant setting. In addition, selection bias according to age, sex, tumor location, and therapy selection and other unmeasurable confounding factors could not be controlled, and this marked variability in patient backgrounds prevented us from assessing objective differences between GCis and GCb regimens in terms of clinical outcomes. In this regard, the main purpose of the present study was to evaluate patient-reported QOL, and tumor responses were not suitable to be investigated.

Despite these limitations, to our knowledge we are the first to report the influence of neoadjuvant GCb chemotherapy on patient-reported QOL outcomes in locally advanced UC. Our results reveal a favorable QOL profile in patients treated with the GCb regimen and suggest that this modality may be an effective alternative for patients in whom GCis is not recommended.

In conclusion, both GCis and GCb regimens were feasible in terms of QOL. Although the present study is small and preliminary, the GCb regimen may be associated with a better QOL status especially concerning gastrointestinal symptoms. Further well-designed prospective studies are necessary to confirm the benefit of carboplatin-based neoadjuvant chemotherapy for UC patients.

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