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【 CASE REPORT 】

Fatal Hepatitis C after Chemotherapy in a Patient with Malignant Lymphoma: Possible Reactivation of Seronegative Occult Hepatitis C Virus Infection Due to Chemotherapy

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Abstract:

A 79-year-old man with lymphoma who tested negative for anti-hepatitis C virus (HCV) antibody received rituximab-containing chemotherapy. Liver dysfunction of unknown cause had persisted since the second cycle of chemotherapy. Ten months after treatment, he rapidly developed massive ascites and atrophy of the liver, and we detected HCV RNA in his serum using real time polymerase chain reaction. Furthermore, medical interviews showed that the patient had no episodes for acute HCV infection, but he did have a history of unspecified liver dysfunction. These findings support the possibility of the reactivation of seronegative occult HCV infection due to chemotherapy in a cancer patient.

Key words: hepatitis C virus reactivation, occult hepatitis C virus infection, malignant lymphoma, chemotherapy, R-CHOP therapy

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Introduction

Chemotherapy using cytotoxic agents and targeted antibodies has helped prolong the cancer patient survival in recent years (1-4). However, since many chemotherapeutic drugs are metabolised in the liver and directly hepatotoxic (5), chemotherapy can cause liver injury, which sometimes leads to a poor clinical outcome.

The severity of adverse effects on the liver caused by antineoplastic agents depends on the age, gender, genetic susceptibility, concomitant medications, tumour involvement in the liver and preexisting liver diseases, such as fatty liver, chronic hepatitis and liver cirrhosis (6). In particular, cancer patients with hepatitis viruses have to be carefully treated with chemotherapy, as their impaired hepatic function sometimes precludes the administration of anticancer drugs in standard doses or intervals (7).

A major issue that must be considered when treating hepatitis virus-positive cancer patients is the influence of drugs commonly used in cancer treatments on the clinical outcomes of these patients (8). Hepatitis B virus (HBV) reactivation is an established complication occurring among HBV-positive cancer patients treated with chemotherapeutic drugs (9). Reactivation of HBV replication can become severe, resulting in liver failure and death in some cases. In addition, reactivation of hepatitis C virus (HCV) due to immunosuppressive treatment has also been reported in the literature, although data on the clinical outcomes in cancer patients with HCV receiving such treatment have been controversial (10).

Occult HCV infection (OCI), which was first reported by

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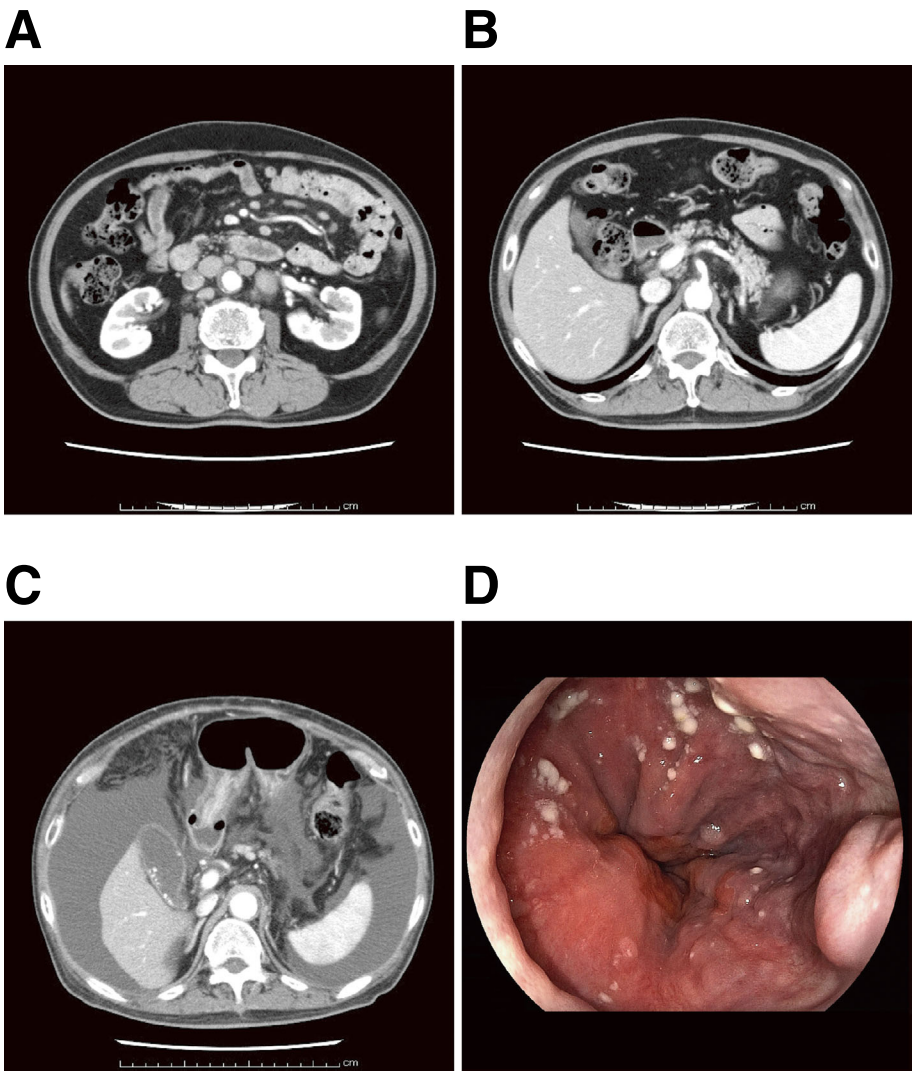

Figure 1. **Imaging tests performed before (A, B) and after (C, D) R-CHOP therapy. (A) Our patient presented with systemic lymphadenopathy, including swollen abdominal paraaortic and mesenteric lymph nodes as shown by computed tomography (CT), before R-CHOP therapy. (B) CT showed no abnormal morphological results in the liver or spleen before R-CHOP therapy. (C) Massive ascites and atrophy of the liver were revealed by CT 10 months after the commencement of R-CHOP therapy. (D) Oesophageal varices were observed using oesophagogastroduodenoscopy 11 months after the treatment.**

two different research groups approximately at the same time in 2004 (11, 12), is a newly recognised mode of HCV infection (13, 14). In individuals with OCI, HCV RNA is undetectable in serum using standard polymerase chain reaction (PCR), whereas HCV is latent in the liver, peripheral blood mononuclear cells (PBMCs) and/or ultracentrifuged serum (11, 12, 15, 16).

OCI is now classified into two different subtypes according to the HCV-related virological and immunological status in serum, i.e. seropositive OCI and seronegative OCI (13, 14). Specifically, individuals with seropositive OCI test positive for anti-HCV antibody and negative for HCV RNA in serum, while those with seronegative OCI negative for both (13). Recently, based on an acknowledged association between HCV infection and haematological diseases (17), several groups have addressed the prevalence of OCI among patients with these diseases (18-21). However, the significance of OCI in the clinical course of patients with haematological tumours has not yet been verified.

We herein report an anti-HCV antibody-negative lymphoma patient who may have exhibited reactivation of seronegative OCI after chemotherapy.

Case Report

A 79-year-old man with follicular lymphoma (grade 3A) was treated with first-line chemotherapy consisting of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) (22). Staging examinations, including a bone marrow biopsy, showed the Ann Arbor stage to be IV. Representative lesions of lymphoma are shown in Fig. 1A. The Follicular Lymphoma International Prognostic Index

Table 1. Results of Blood and Urine Tests Performed before R-CHOP Therapy.

Parameter	Value	Unit	Reference value	Parameter	Value	Unit	Reference value	Parameter	Value	Unit	Reference value
Blood cell count				Biochemistry				Immunology			
WBC	4.1	$\times10^3/\mu L$	3.3-8.6	TP	7.5	g/dL	6.6-8.1	CRP	0.11	mg/dL	0.00-0.14
St	1	%	0-6	Alb	66.4	%	55.8-66.1	IgG	1,116	mg/dL	861-1,747
Seg	72	%	32-73	$\alpha1$	2.9	%	2.9-4.9	IgA	166	mg/dL	93-393
Ly	20	%	25-45	$\alpha2$	8.9	%	7.1-11.8	IgM	96	mg/dL	33-183
Mo	6	%	4-7	β	8.0	%	7.9-13.7	HBs Ag	(-)		(-)
Eo	1	%	1-5	γ	13.8	%	11.1-18.8	HBs Ab	(-)		(-)
Ba	0	%	0-2	Alb	4.7	g/dL	4.1-5.1	HBc Ab	(-)		(-)
RBC	4.47	$\times10^6/\mu L$	4.35-5.55	BUN	21.9	mg/dL	8.0-20.0	HCV Ab	(-)		(-)
Hb	13.7	g/dL	13.7-16.8	Cr	0.6	mg/dL	0.65-1.07	HIV Ab	(-)		(-)
Ht	39.9	%	40.7-50.1	UA	4.3	mg/dL	3.7-7.8	HTLV-1 Ab	<16	times	<16
MCV	89.3	fL	83.6-98.2	Na	139	mEq/L	138-145	Anti-nuclear Ab	<40	times	<40
MCH	30.6	pg	27.5-33.2	Cl	103	mEq/L	101-108				
MCHC	34.3	%	31.7-35.3	K	4.3	mEq/L	3.6-4.8	Tumour marker			
Ret	7	‰	2-26	Ca	9.3	mg/dL	8.8-10.1	β2-MG	2.3	mg/L	1.0-1.9
Plt	201	$\times10^3/\mu L$	158-348	T-Bil	0.6	mg/dL	0.4-1.5	sIL-2R	956	U/mL	122-496
				D-Bil	0.1	mg/dL	0.0-0.3				
Coagulation				AST	22	IU/L	13-30				
PT	12.0	sec	9.8-12.1	ALT	13	IU/L	10-42				
	92	%	70-130	LDH	209	IU/L	124-222				
	1.02	ratio	0.85-1.15	ALP	245	IU/L	106-322				
APTT	27.1	sec	24.0-39.0	γ-GTP	38	IU/L	13-64				
Fib	228	mg/dL	200-400	ChE	335	IU/L	240-486				
ATIII	82	%	80-130	Amy	125	IU/L	44-132				
FDP	0.2	μg/mL	<5.0	CPK	59	IU/L	59-248				
D-D dimer	0.6	μg/mL	<1.0	Glu	108	mg/dL	73-109				
				HbA1c	5.5	%	4.3-5.8				
				T-Chol	245	mg/dL	142-248				
Urinanalysis				LDL	131	mg/dL	65-163				
Protein	(-)		(-)	TG	315	mg/dL	40-234				
Glu	(-)		(-)	Fe	107	μg/dL	54-200				
OB	(-)		(-)	Ferritin	72	ng/mL	10-250				
Bil	(-)		(-)	TIBC	291	μg/dL	253-365				

WBC: white blood cell, RBC: red blood cell, Hb: haemoglobin, Ht: haematocrit, MCV: mean corpuscular volume, MCH: mean corpuscular haemoglobin, MCHC: mean corpuscular haemoglobin concentration, Ret: reticulocyte, Plt: platelet, PT: prothrombin time, APTT: activated partial thromboplastin time, Fib: fibrinogen, ATIII: antithrombin III, FDP: fibrin and fibrinogen degradation product, Glu: glucose, OB: occult blood, Bil: bilirubin, TP: total protein, Alb: albumin, BUN: blood urea nitrogen, Cr: creatinine, UA: uric acid, T-Bil: total bilirubin, D-Bil: direct bilirubin, AST: aspartate transaminase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, γ-GTP: γ-glutamyl transpeptidase, ChE: cholinesterase, Amy: amylase, CPK: creatine phosphokinase, HbAlc: haemoglobin Alc, T-Chol: total cholesterol, LDL: low-density lipoprotein, TG: triglycerides, TIBC: total iron binding capacity, CRP: C-reactive protein, IgG: immunoglobulin G, IgA: immunoglobulin A, IgM: immunoglobulin M, HBs Ag: hepatitis B surface antigen, HBs Ab: anti-hepatitis B surface antibody, HBc Ab: anti-hepatitis B core antibody, HCV Ab: anti-hepatitis C virus antibody, HIV Ab: anti-human immunodeficiency virus antibody, HTLV-1 Ab: anti-human T-lymphotropic virus type-1 antibody, Anti-nuclear Ab: anti-nuclear antibody, β2-MG: β2-microglobulin, sIL-2R: soluble interleukin-2 receptor

was judged to be high risk.

Blood and imaging tests found no abnormal results in his liver function, hepatitis virus status and appearance of the liver before chemotherapy (Table 1, Fig. 1B). In particular, the aspartate transaminase (AST) to Platelet Ratio Index (APRI) (23) and Fibrosis-4 (FIB-4) (24) were 0.365 and 2.40, respectively. Computed tomography did not show splenomegaly. No oesophageal varices were observed using oesophagogastroduodenoscopy (data not shown).

His disease responded well to the treatment, although mild liver dysfunction occurred after the administration of the second cycle of R-CHOP therapy (Fig. 2). During the fifth cycle of the therapy, a fever, neutropenia and further liver injury developed (Fig. 2). He was diagnosed with febrile neutropenia and treated with antibiotics. Neither bacteraemia nor cytomegalovirus (CMV) viraemia was documented by blood culture tests or other evaluations. He gradually recovered from the fever and neutropenia, but his moderate liver dysfunction remained (Fig. 2).

As there were no apparent causes of liver dysfunction and the possibility of drug-induced liver injury was considered, all drugs used in R-CHOP therapy were discontinued four

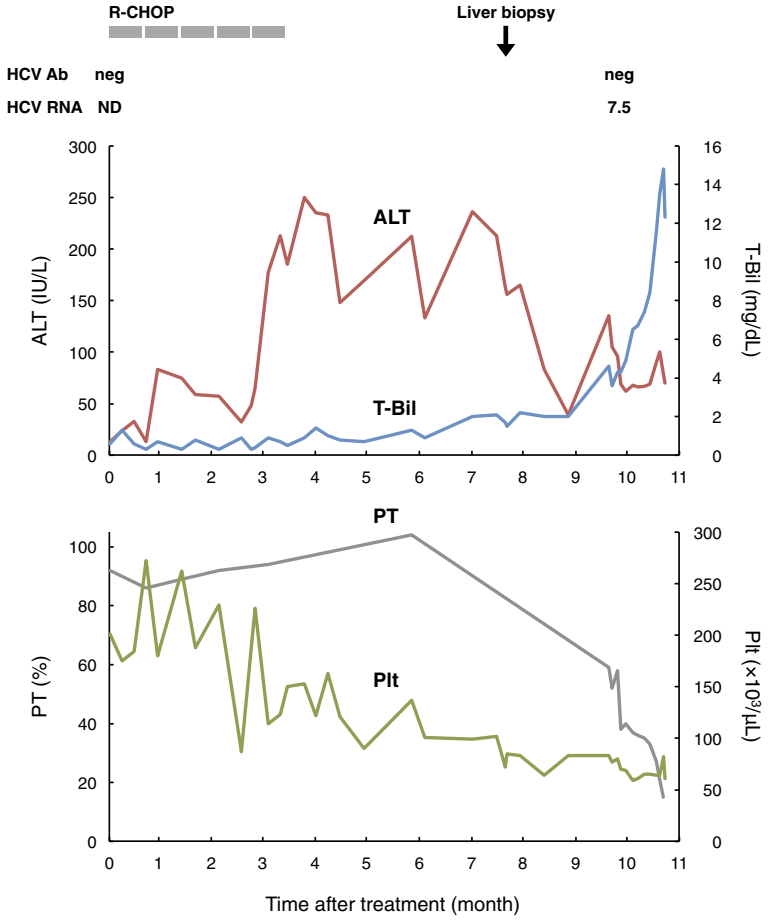

Figure 2. Clinical course of possible occult hepatitis C virus reactivation and liver failure during treatment. Results representative for the events are shown as follows: red line: serum alanine aminotransferase (ALT), blue line: serum total bilirubin (T-Bil), grey line: plasma prothrombin activity (PT), green line: blood platelet (Plt), grey box: one cycle of R-CHOP therapy, arrow: liver biopsy, HCV Ab: anti-hepatitis C virus (HCV) antibody, HCV RNA: HCV RNA determined using real time PCR (log IU/mL), ND: no data, neg: negative

months after the initiation of R-CHOP therapy. Nevertheless, the moderate liver dysfunction was not ameliorated (Fig. 2). Serum hepatitis-related tests, including HBV DNA, were thus conducted seven months after the treatment and showed no abnormal results (Table 2). Abdominal ultrasonography and magnetic resonance imaging/cholangiopancreatography also exhibited no significant findings except for slight ascites, in which no malignant cells were detected by cytology.

Since moderate liver dysfunction persisted, a liver biopsy was next performed eight months after the therapy (Fig. 2). The tissue specimen revealed acute-on-chronic liver injury (Supplemental material). Hepatocytes widely represented swollen and pale cytoplasm. Moderate to severe mononuclear infiltrates were seen in the portal tract and liver parenchyma. Expansion of the portal tract with mild bridging fibrosis was associated. These histopathological features corresponded to chronic-active hepatitis, i.e. A2F2 according to the new Inuyama Classification. In addition to this, the acidophilic bodies were scattered, and centrilobular necrosis with haemorrhaging was observed, thus suggesting a flare-up of hepatitis. No infiltrated lymphoma cells were observed in the liver specimen using immunohistochemistry for CD20.

Ten months after the commencement of R-CHOP therapy, surprisingly, massive ascites and atrophy of the liver rapidly occurred (Fig. 1C). Therefore, we again examined the hepatitis-related virological and immunological status in serum, including the infectious status for HBV, HCV and CMV. Intriguingly, anti-HCV antibody was again found to be negative by a third-generation chemiluminescent enzyme immunoassay, whereas HCV RNA was detected in his serum using real time PCR (7.5 log IU/mL) (Table 2, Fig. 2). The HCV genotype was untested.

We therefore asked the patient some medical questions relevant to hepatitis in detail. His answers showed that he had no episodes potentially involved with the recent occurrence of acute HCV infection, such as blood transfusion, needle-stick exposure and sexual activity, before and during treatment (25). Furthermore, through our interviews, he finally recollected that he had been diagnosed with liver dysfunction approximately 20 years before. We unfortunately

Table 2. Hepatitis-related Virological and Immunological Status in Our Patient's Serum before and after R-CHOP Therapy.

Parameter	Value	Unit	Reference value
Before treatment			
HBs Ag	(-)		(-)
HBs Ab	(-)		(-)
HBc Ab	(-)		(-)
HCV Ab	(-)		(-)
ANA	<40	times	<40
IgG	1,116	mg/dL	861-1,747
IgA	166	mg/dL	93-393
IgM	96	mg/dL	33-183
7 months after treatment			
HBs Ag	(-)		(-)
HBV DNA (real time PCR)	ND	log copies/mL	ND
ANA	<40	times	<40
AMA-M2	<5	U/mL	<7
SMA	<40	times	<40
IgG	975	mg/dL	861-1,747
IgA	144	mg/dL	93-393
IgM	69	mg/dL	33-183
10 months after treatment			
HCV Ab	(-)		(-)
HCV RNA (real time PCR)	7.5	log IU/mL	ND
HCV serological group	Undetermined		
HBs Ag	0.03	IU/mL	<0.05
HBV DNA (real time PCR)	ND	log copies/mL	ND
ANA	<40	times	<40
AMA-M2	<5	U/mL	<7
SMA	<40	times	<40
IgG	1,158	mg/dL	861-1,747
IgA	220	mg/dL	93-393
IgM	97	mg/dL	33-183
CMV pp65 Ag (HRP-C7)	ND		ND

AMA-M2: anti-mitochondrial M2 antibody, ANA: anti-nuclear antibody, CMV pp65 Ag: cytomegalovirus pp65 antigen, DNA: deoxyribonucleic acid, HBc Ab: anti-hepatitis B core antibody, HBs Ab: anti-hepatitis B surface antibody, HBs Ag: hepatitis B surface antigen, HBV: hepatitis B virus, HCV: hepatitis C virus, HCV Ab: anti-hepatitis C virus antibody, HRP-C7: assay for CMV using a horseradish peroxidase-conjugated monoclonal antibody C7, IgA: immunoglobulin A, IgG: immunoglobulin G, IgM: immunoglobulin M, ND: not detected, PCR: polymerase chain reaction, RNA: ribonucleic acid, SMA: anti-smooth muscle antibody

were unable to obtain the details of his medical history concerning liver dysfunction, since his memory was vague.

These findings implied that he may have had seronegative OCI before R-CHOP therapy, with reactivation of HCV, particularly seronegative OCI, possibly occurring consequently due to the treatment. He received best supportive care without antiviral therapy according to his wishes, ultimately succumbing to liver failure 11 months after R-CHOP therapy (Fig. 2).

Discussion

Recently, the two subtypes of OCI have bene considered to be caused by different mechanisms involved with the exposure and clearance of HCV. Seropositive OCI is frequently observed as a result of the resolution of clinically evident chronic hepatitis C by antiviral therapy (12, 15, 26). Seronegative OCI, by contrast, may be caused by asymptomatic exposure to HCV, at least in some individuals, and may be followed by spontaneous clearance of HCV from the serum and the subsequent disappearance of serum anti-HCV antibody over time (27-29). In our patient, anti-HCV antibody had been undetectable before and during treatment, but serum HCV RNA was finally detected in the final phase (Table 2). Unfortunately, we were unable to confirm whether or not HCV RNA had been present in his serum, liver and/or PBMCs before treatment, since there were no available samples. However, considering the high sensitivity and specificity of the chemiluminescent enzyme immunoassay for serum anti-HCV antibody (30), our patient was very unlikely to have had HCV RNA, at least in his serum, before treatment, unless he had been in an early stage of acute

HCV infection. Indeed, our interviews with the patient turned up no opportunities for the patient to have been newly infected with HCV (25) before or during treatment.

Of note, serum anti-HCV antibody can show a false negative in patients with immunocompromised diseases, such as human immunodeficiency virus-1 infection and renal failure (31-34). However, since the present patient had no such diseases before treatment, his anti-HCV antibody was almost certainly a true negative. Taken together, these findings suggest that our patient did not have HCV RNA in his serum before treatment.

In addition, our medical interviews also revealed that our patient had had a history of unspecified liver dysfunction occurring approximately two decades earlier, suggesting that the patient had been infected with HCV long before this presentation, with the virus resolving spontaneously over time and lying latent in his liver and/or PBMCs before undergoing chemotherapy. Indeed, a few individuals have seronegative OCI regardless of underlying diseases (11, 18-21, 35-41). These findings support the possibility of seronegative OCI in our patient (14).

Reactivation of HCV does occur in HCV-positive cancer patients treated with antineoplastic agents (42). In particular, rituximab, one of the most important chemotherapeutic drugs for lymphoma patients (4), causes HCV reactivation and liver damage (42-44) through immunosuppression after the initiation of rituximab-containing chemotherapy and subsequent immune recovery after the discontinuation of the treatment (10, 45). Severe liver dysfunction caused by immunosuppressive treatment such as chemotherapy occurs less frequently in patients with HCV than in those with HBV (10, 46). However, once severe hepatitis develops following viral reactivation, the mortality rate seems to be similar between HBV- and HCV-positive patients (47, 48). Reactivation and proliferation of HCV generally begins to occur two to four weeks after chemotherapy, damaging the liver and occasionally resulting in a poor patient outcome (10). Indeed, the clinical course of our patient was quite similar to those of patients who developed reactivation of HCV (49) or resolved HBV infection (50) (Fig. 1C, D, 2). Due to chemotherapy, the HCV that was latent in our patient's liver and/or PBMCs may have reactivated and proliferated, injuring the liver and thus eventually causing liver failure.

In conclusion, although the possibility that our patient's event was caused by the recent occurrence of acute hepatitis C still remains, our findings seem to imply the possibility of hitherto unrecognised reactivation of resolved HCV infection, i.e. seronegative OCI, in a clinical course of cancer. At present, there are no useful ways to detect seronegative OCI using commercially available assays. Thus, it is crucial to consider the possibility of reactivation of seronegative OCI if an anti-HCV antibody-negative cancer patient treated with chemotherapy suffers from liver injury of unknown origin.

We should verify this disease in a larger cohort in order to confirm and generalise the results and treatment of this event. The development of useful and convenient assay techniques for OCI is also necessary. These efforts may lead to the establishment of reliable predictive markers and, consequently, to truly personalised approaches for the more effective treatment of cancer patients.

The authors state that they have no Conflict of Interest (COI).

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