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Response to targeted therapy or chemotherapy following immunotherapy in patients with gastrointestinal cancers - a case series

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Abstract

Background: In non-small cell lung cancer, response rates to chemotherapy given after immune checkpoint inhibitors has been reported to be higher compared to response rates to chemotherapy given before immune checkpoint inhibitors. However, this phenomenon has not been reported in patients with gastrointestinal cancers nor with the use of multi-targeted kinase inhibitors.

Case presentation: We present a series of six patients who received multi-targeted kinase inhibitors or chemotherapy after progression on immune checkpoint inhibitors and showed unexpected response. Five of these patients had metastatic hepatocellular carcinoma and received salvage multi-targeted kinase inhibitors. Two of these five patients had no response to initial multi-targeted kinase inhibitors but had unexpected response to re-challenge with multi-targeted kinase inhibitors after immune checkpoint inhibitors exposure. The sixth patient had metastatic rectal cancer and showed response to salvage chemotherapy following immune checkpoint inhibitors.

Conclusion: We postulate that the sequencing of immune checkpoint inhibitors prior to other forms of systemic therapy may potentially lead to an immunomodulatory effect in gastrointestinal cancers with potential improvement in response rates.

Keywords: Immunotherapy, Targeted therapy, Gastrointestinal cancers

Background

The introduction of immune checkpoint inhibitors (ICI) has redefined how we treat cancer in recent years, and has been approved for use in multiple tumour types in the advanced setting for second-line treatment or later, and also as first line treatment in non-small cell lung cancer (NSCLC) in patients with high PDL-1 expression [1]. Interesting response patterns have been observed in patients receiving immunotherapy including that of hyper-progressive disease as well as pseudo-progression. Another recently described phenomenon includes the improved response rates of systemic treatment given post-ICI [2]. This has been described in several case series in NSCLC with patients receiving chemotherapy post-ICI showing unexpectedly high response rates (RR) [3] [4, 5]. A patient with malignant melanoma, a cancer traditionally considered chemotherapy resistant, was also reported to have shown unexpected response to dacarbazine and cisplatin combination chemotherapy after initial treatment and non-response to prior targeted therapies and ICI [6]. Similar excellent and unexpected responses to chemotherapy after exposure to ICIs have also been described in reports of patients with other cancer types including that of metastatic squamous cell carcinoma and B-cell lymphoma [7].

To the best of our knowledge, this phenomenon however has not been reported in gastrointestinal cancers or with the use of multi-targeted kinase inhibitors (MKI). Here we present a case series of six patients with gastrointestinal cancers who progressed on ICI treatment and

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subsequently received chemotherapy or MKI with better than expected response, of which five patients had advanced hepatocellular carcinoma (HCC) and received MKI post-ICI.

Case presentation

Case 1

A 66-year-old male patient was first diagnosed with early HCC in July 2016 and underwent surgical resection. His disease recurred locally 11 months later and he underwent transarterial chemoembolization (TACE) twice in June and July 2017. Despite this, his disease continued to progress and he was started on sorafenib in October 2017. A scan in January 2018 showed interval increase in the size of liver lesions and he was switched to a PD-1 inhibitor, receiving three doses between January 2018 and end February 2018. Clinically and radiologically his disease progressed, and after discussion, he decided for a re-challenge with sorafenib in April 2018 while awaiting possible availability for enrollment into a clinical trial. Surprisingly, a repeat scan in May 2018 showed treatment response with some lesions smaller and some resolved (Fig. 1). He continues to be on sorafenib as of end March 2019 with continued response at more than 50.4 weeks after re-challenge.

Case 2

A 63-year-old male patient with Child-Pugh A hepatitis B liver cirrhosis was diagnosed with HCC in November 2016. He underwent a segmental resection of segment 5 as well as radiofrequency ablation (RFA) of lesions in segments 6 and 7 in December 2016. After five months, he unfortunately developed new liver lesions as well as peritoneal metastases in April 2017. He enrolled into a clinical trial and was randomized to the arm receiving an oncolytic virus vaccine followed by sorafenib. He received the treatment between July 2017 and August 2017 but had early clinical and radiological progression and was taken off trial. He managed to enroll into a second clinical trial in September 2017 on which he received a combination of a FGFR inhibitor and a PD-1 inhibitor. After five months, his disease progressed in February 2018 and was taken off trial and switched to the MKI lenvatinib. Interval scan in May 2018 showed a partial response of his cancer, and he continued to show clinical response for a total of 18 weeks after initiation of lenvatinib (Fig. 2). In July 2018, his disease progressed and he was started on the monoclonal antibody, Ramucirumab. Interval scan in October 2018 showed partial response. His disease progressed in January 2019 and he received 1 cycle of Capecitabine and Oxaliplatin. In view of his worsening liver function and clinical progression, he stopped treatment since February 2019 and has been on best supportive care since.

Case 3

A 68-year-old male patient with Child-Pugh A hepatitis B liver cirrhosis was first diagnosed with HCC in 2010 for which he underwent surgical resection. He recurred with liver lesions and pelvic lymphadenopathy in May 2017 and was enrolled into a clinical trial on which he received a PD-L1 inhibitor from July 2017. An initial CT scan in December 2017 showed interval decrease in size of the liver mass, with stable abdominopelvic adenopathy. However, in February 2018, he showed clinical and radiological progression of disease with increase in both the liver lesions and abdominopelvic lymphadenopathy. He was taken off trial in the same month and switched to sorafenib. A repeat CT scan in April 2018 showed partial response with decrease in size and arterial enhancement of the main hepatic mass, in addition to stable abdominopelvic adenopathy and improvement in ascites (Fig. 3). Unfortunately, a subsequent scan in mid-June 2018 showed disease progression and he was switched to lenvatinib. He had progression of disease in August 2018, and was switched to regorafenib, though this was stopped 4 weeks after initiation in view of worsening liver function. He passed away in September 2018.

Case 4

A 68-year-old male patient with known Child-Pugh A hepatitis C liver cirrhosis was diagnosed with HCC in

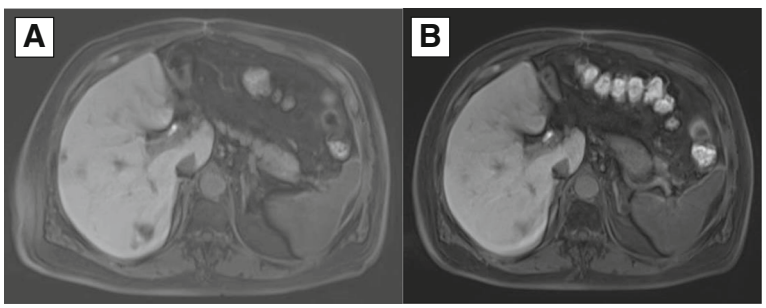

Fig. 1 **a** Magnetic Resonance Imaging (MRI) scan in March 2018 after treatment with a PD-1 inhibitor. **b** MRI scan showing smaller lesions in May 2018 after treatment with Sorafenib

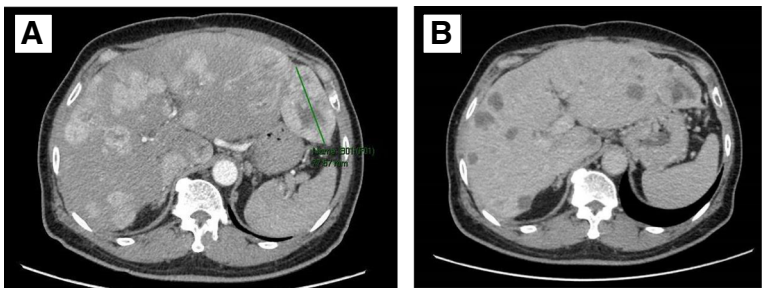

Fig. 2 a Computed Tomography (CT) scan in February after treatment with an FGFR inhibitor and a PD-1 inhibitor. **b** CT scan showing smaller lesions in May 2018 after treatment with Lenvatinib

2014. Between March 2014 and 2017, he underwent TACE of his liver lesions thrice. Upon progression, he was enrolled into a clinical trial and received a PD-L1 inhibitor. His disease progressed with new lung metastases after 12.2 weeks. He was enrolled onto a Phase 1 clinical trial and received an RNA oligonucleotide drug, MTL-CEBPA and progressed clinically and radiologically after 6.9 weeks. Bland embolization was performed to a symptomatic liver lesion and sorafenib was initiated. Complete response was seen on interval scans at 18.6 weeks. Despite holding off sorafenib due to toxicities, there was no further disease progression (Fig. 4). Sorafenib was restarted in October 2018 with continued response as of 30 March 2019.

Case 5

A 60-year-old male patient with Child-Pugh A hepatitis B liver cirrhosis was diagnosed with HCC in April 2016. Following disease progression post-TACE and surgical resection, he was enrolled into a clinical trial and randomized into the arm receiving combination immunotherapy with a CTLA-4 and PD-L1 inhibitor. His disease progressed further at 16.4 weeks. He was switched to a phase 1 trial and started on the RNA oligonucleotide drug, MTL-CEBPA. Following further progression clinically and radiologically after 8 weeks, treatment was switched to lenvatinib. There was sustained partial response in target lesions in the liver for 20.4 weeks (Fig. 5). In view of further disease progression, he was enrolled in a clinical trial and randomized into the arm receiving a pan-HER inhibitor. His disease progressed at 3.1 weeks and he was enrolled into another clinical trial and started on an FGFR inhibitor. He passed away after 2.6 weeks.

Case 6

A 79-year-old male patient was first diagnosed with metastatic rectal cancer with liver metastases in 2014. No mutations were detected on genetic profiling for KRAS, NRAS, and BRAF and DNA mismatch repair status was proficient. He was initiated on FOLFOX (5-fluorouracil, oxaliplatin, leucovorin) and cetuximab with continued partial response after cycle 9 and then deescalated to deGramont regimen with cetuximab in view of oxaliplatin-related peripheral neuropathy. Following 8 cycles however, scans showed radiological progression and he was switched to FOLFIRI (5-fluorouracil, irinotecan, leucovorin) and bevacizumab in January 2016 of which he received 16 cycles till January 2017 when repeat scans showed disease progression. He was started on regorafenib in February 2017 but stopped treatment shortly after because of intolerance. He was enrolled in a clinical trial in March 2017 and randomized into an arm receiving a pan-HER inhibitor with FOLFIRI. Again, he tolerated this regimen poorly and was taken off trial and started on TAS-102. He received this from May to July

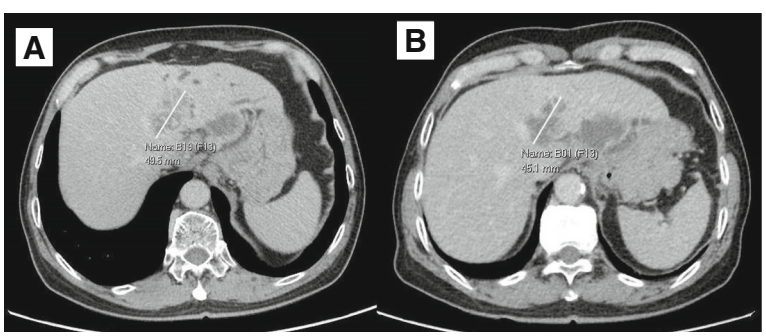

Fig. 3 a: Computed Tomography (CT) scan in February after treatment with a PD-L1 inhibitor. **b**: CT scan showing smaller lesions in April 2018 after treatment with Sorafenib

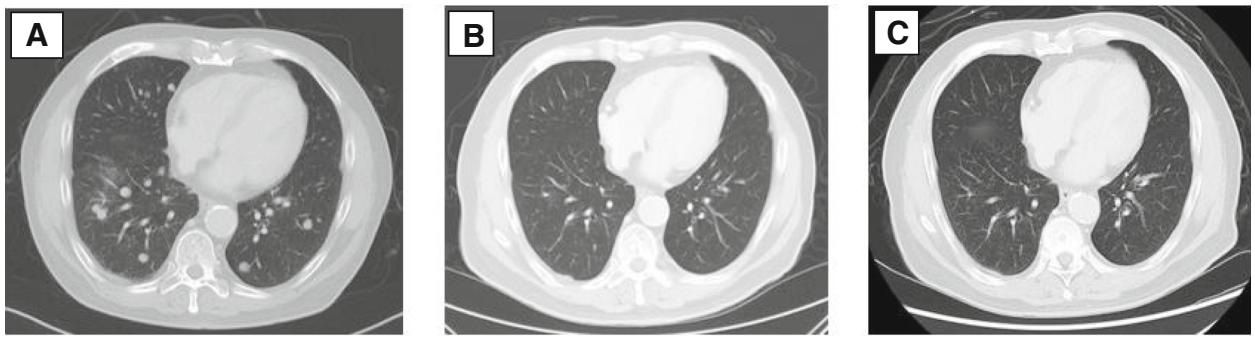

Fig. 4 a: CT scan after treatment with an RNA oligonucleotide drug, MTL-CEBPA. **b**: CT scan showing smaller lesions in March 2018 after treatment with Sorafenib. **c**: CT scan showing continued response 8 weeks after sorafenib was stopped

2017 when a CT scan showed further progression of disease. He was enrolled into a second clinical trial on which he received a combination of a PD-1 inhibitor and a MEK inhibitor from August 2017 till November 2017 when repeat CT scan showed disease progression. After much discussion, he was keen for a re-challenge of FOLFIRI and cetuximab and started this in November 2017. He responded both clinically and radiologically initially and this was sustained for 39.1 weeks (Fig. 6). Unfortunately, a repeat CT scan in September 2018 showed disease progression. He subsequently received Yttrium-90 (Y90) Selective Internal Radiation Therapy (SIRT) to his liver metastases as his disease was largely confined to his liver. He was started on FOLFOX and panitumumab in February 2019. Response has yet to be evaluated as of 30 March 2019 Table 1.

Discussion

The introduction of ICI has changed the landscape of cancer treatment. With their impressive results in the late line setting, there are multiple ongoing trials trying to study the position of ICI earlier in the treatment continuum. Increasing efforts are hence being made to investigate and understand the role of sequencing and combination of immunotherapy with other systemic treatment options of chemotherapy and/ or targeted therapy to capitalise on possible synergistic immune effects on tumour microenvironment [8].

Anecdotally, this has been suggested through several case series. A retrospective study by Park et al. comparing the objective response rates (ORR) of salvage chemotherapy after immunotherapy (SCAI) in NSCLC with the ORRs after the last chemotherapy before immunotherapy (LCBI) in 73 patients showed a significantly higher ORR for SCAI of 53.4% compared to the ORR of LCBI at 34.9% [3]. This was supported Grigg et al's report of 39 patients with NSCLC who received chemotherapy after administration of immune checkpoint inhibitors with an unexpectedly high ORR [4] as well as Leger et al's reported of 67 patients with NSCLC which showed that those with prior exposure to anti PD-1/PDL-1 inhibitors were three times more likely to achieve a partial response to salvage chemotherapy compared with patients who had not been treated with PD-1/PDL-1 inhibitors [5].

The outcomes of salvage systemic therapy after immunotherapy in gastrointestinal malignancies however,

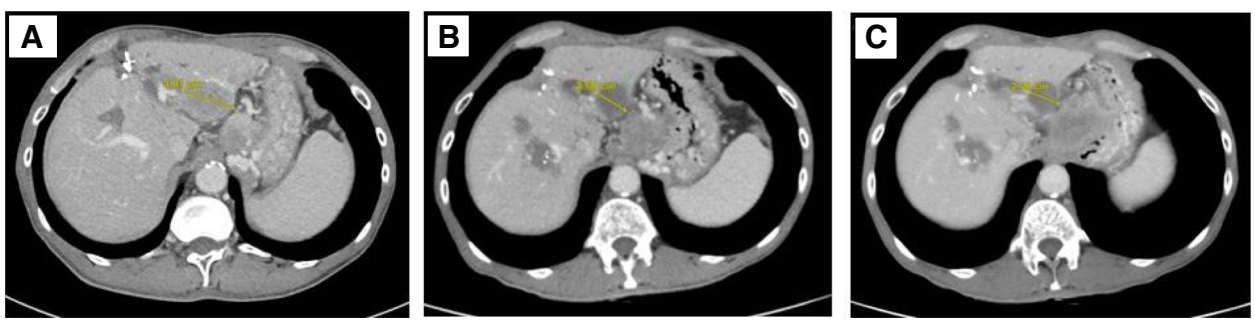

Fig. 5 a CT scan after treatment with an RNA oligonucleotide drug, MTL-CEBPA; 4.0 cm liver lesion **b** CT scan showing partial response after treatment with Lenvatinib for 8 weeks; 2.6 cm liver lesion **c** CT scan showing continued response after treatment with Lenvatinib for 20.4 weeks; 2.3 cm liver lesion

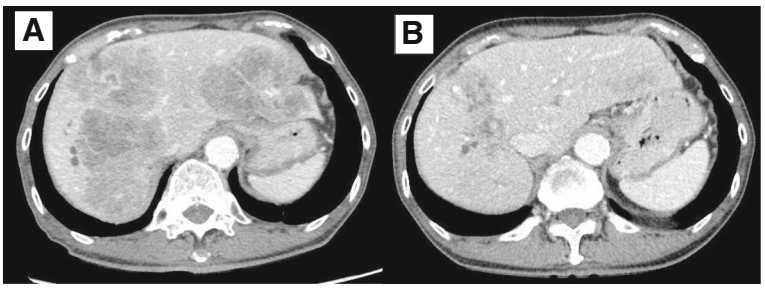

Fig. 6 a Computed Tomography (CT) scan in November 2017 after treatment with a PD-1 inhibitor. **b** CT scan showing smaller lesions in March 2018 after re-challenge with FOLFIRI and cetuximab

have not been previously well-described. Nivolumab was granted conditional approval by the United States FDA for use as a second-line treatment for advanced HCC after impressive results in the phase 1/2 Checkmate-040 study [9]. Both pembrolizumab and nivolumab have also shown been used in microsatellite instability-high or deficient mismatch repair metastatic colorectal cancer that has progressed following conventional chemotherapy [10, 11].

Conclusion

This case series suggests that salvage targeted therapy or chemotherapy may also be more effective following immunotherapy in the setting of gastrointestinal malignancies and suggests that earlier initiation of immunotherapy may positively modulate responses to outcomes with other systemic treatment options. Interestingly, the first two patients in the case series with HCC showed no response to initial treatment with first use of targeted therapy, but demonstrated unexpected response to salvage rechallenge with targeted therapy after immunotherapy exposure, further supporting the theory of a possible change in the tumour microenvironment after interim exposure with ICI. The possible mechanism underlying this observed phenomenon is as yet unclear. While pseudo-progression following ICI has been reported in less than 10 % of cancers treated with immunotherapy, none of the cases presented in this series met the criteria for pseudo-progression as subsequent imaging confirmed progressive disease.

While this case series offers promising insight into the potential benefits of such sequencing and possibly combination therapy of ICI and targeted therapy in advanced gastrointestinal cancers, additional studies are required. A systematic review to better characterise the prevalence of this phenomenon and to evaluate impact on

Table 1 Summary of Treatment Received for Patients in Case Series

Primary Diagnosis	Systemic treatment received before ICI (best response, progression free survival)	ICI received (best response, progression free survival)	Systemic treatment received post ICI (best response, progression free survival)
Case 1 HCC (uninfected)	Sorafenib (SD, 17.3 weeks)	PD-1 inhibitor (PD, 6.9 weeks)	Sorafenib (PR, 50.4 weeks[b])
Case 2 HCC (Child-Pugh A Hepatitis B)	Oncolytic vaccine and sorafenib[a] (PD, 11.7 weeks)	FGFR inhibitor and PD-1 inhibitor (SD, 21.1 weeks)	Lenvatinib (PR, 18.0 weeks) Ramucirumab (PR, 24.0 weeks) XELOX (PD, 4.0 weeks)
Case 3 HCC (Child-Pugh A Hepatitis B)	None	PD-L1 inhibitor (SD, 31.0 weeks)	Sorafenib (PR, 14.7 weeks); Lenvatinib (PD, 7.0 weeks) Regorafenib (PD, 4.0 weeks)
Case 4 HCC (Child-Pugh A Hepatitis C)	None	PD-L1 inhibitor (SD, 12.2 weeks)	Sorafenib (CR, 65.4 weeks[b])
Case 5 HCC (Child-Pugh A Hepatitis B)	None	PD-L1 inhibitor CTLA-4 inhibitor (PD, 16.4 weeks)	Lenvatinib (PR, 20.4 weeks) Pan-HER inhibitor (PD, 3.1 weeks) FGFR inhibitor (NE, 2.6 weeks)
Case 6 Rectal cancer	FOLFOX-Cetuximab ➔ deGramont-Cetuximab (PR, 55.9 weeks) FOLFIRI-Bevacizumab (PR, 55.6 weeks) Regorafenib (NE) FOLFIRI/ Pan-Her inhibitor (NE) TAS-102 (PD, 9.6 weeks)	PD-1 inhibitor and MEK inhibitor (SD, 12.1 weeks)	FOLFIRI and cetuximab (PR, 39.1 weeks) FOLFOX and panitumumab (NE)

SD stable disease, *PD* progressive disease, *PR* partial response, *NE* not evaluated
[a] Sorafenib started after completion of vaccine; duration of sorafenib: 4.7 weeks
[b] Ongoing response as of 30 March 2019

progression-free survival and overall survival, in addition to response rates is planned.

Abbreviations

CT: Computed tomography; FOLFIRI: 5-fluorouracil, irinotecan, leucovorin; FOLFOX: 5-fluorouracil, oxaliplatin, leucovorin; HCC: Hepatocellular carcinoma; ICI: Immune checkpoint inhibitors; LCBI: Last chemotherapy before immunotherapy; MKI: Multi-targeted kinase inhibitors; MRI: Magnetic Resonance Imaging; NE: Not evaluated; NSCLC: Non-small cell lung cancer; ORR: Objective response rates; PD: Progressive disease; PR : Partial response; RFA: Radiofrequency ablation; RR: Response rates; SCAI: Salvage chemotherapy after immunotherapy; SD: Stable disease; SIRT : Selective internal radiation therapy; TACE: Transarterial chemoembolization; XELOX: oxaliplatin, capecitabine; Y90: Yttrium-90

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Authors' contributions

All authors contributed to the collection of data and writing of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

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Ethics approval and consent to participate

This study was approved by the Singhealth Centralised Institutional Review Board (CIRB).

Consent for publication

Consent for publication was obtained from all participants.

Competing interests

The authors declare that they have no competing interests.

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