BRIEF REPORT

Increased Hepatotoxicity Associated with Sequential Immune Checkpoint Inhibitor and Crizotinib Therapy in Patients with Non–Small Cell Lung Cancer

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Received 27 July 2018; revised 18 August 2018; accepted 1 September 2018
Available online - 8 September 2018

ABSTRACT

Introduction: Immune checkpoint inhibitors (ICIs) are standard therapies in advanced NSCLC. Although genotype-directed tyrosine kinase inhibitors represent the standard of care for subsets of oncogene-driven NSCLC, patients may receive ICIs during their disease course. The impact of sequential ICI and tyrosine kinase inhibitor therapy on the risk of hepatotoxicity has not been described.

Methods: Patients with advanced ALK receptor tyrosine kinase (ALK)-driven, ROS1-driven, or MET proto-oncogene, receptor tyrosine kinase (MET)-driven NSCLC treated with crizotinib, with or without preceding ICI therapy, were identified. The cumulative incidences of crizotinib-associated grade 3 or higher increases in transaminase level (per the Common Terminology Criteria for Adverse Events, version 4.0) were compared.

Results: We identified 453 patients who had NSCLC with an oncogenic alteration in ALK receptor tyrosine kinase gene (*ALK*), *ROS1*, or MET proto-oncogene, receptor tyrosine kinase gene (*MET*) and were treated with crizotinib (11 with and 442 without prior ICI therapy). Among the 11 patients treated with an ICI followed by crizotinib, five (cumulative incidence 45.5% [95% confidence interval (CI): 14.9–72.2]) experienced development of a grade 3 or 4 increase in alanine transaminase level and four (cumulative incidence 36.4% [95% CI: 10.0–64.2]) experienced development of a grade 3 or 4 increase in aspartate transaminase level. In comparison, among the 442 patients who received crizotinib only, a grade 3 or 4 increase in alanine transaminase level occurred in 34 patients (cumulative incidence 8.1% [95% CI: 5.7–11.0, $p < 0.0001$]) and a grade 3 or 4 increase in aspartate transaminase level occurred in 14 (cumulative incidence 3.4% [95% CI: 1.9–5.5, $p < 0.0001$]). There were no grade 5 transaminitis events. All cases of hepatotoxicity after sequential ICI and crizotinib use were reversible and nonfatal, and no case met the Hy's law criteria.

Conclusions: Sequential ICI and crizotinib treatment is associated with a significantly increased risk of hepatotoxicity. Careful consideration and monitoring for hepatotoxicity may be warranted in patients treated with crizotinib after ICI therapy.

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Disclosures: Dr. Lin has received honorarium from Chugai Pharma and Boehringer Ingelheim. Dr. Sequist has served as a compensated consultant for AstraZeneca, Merrimack, Genentech, Novartis, Pfizer, Bristol-Myers Squibb, and Boehringer Ingelheim. Dr. Heist has served as a compensated consultant for Boehringer Ingelheim and Tarveda. Dr. Mino-Kenudson has served as a compensated consultant for Merrimack Pharmaceuticals and H3 Biomedicine. Dr. Gainor has served as a compensated consultant or received honoraria from Bristol-Myers Squibb, Genentech, Ariad/Takeda, Loxo, Pfizer, Incyte, Novartis, Merck, Agios, Amgen, Regeneron, Oncorus, Array, and Clovis Oncology. Dr. Shaw has served as a compensated consultant or received honoraria from Pfizer, Novartis, Genentech/Roche, Ariad/Takeda, Ignyta, LOXO, Blueprint Medicines, KSQ Therapeutics, Daiichi Sankyo, EMD Serono, Taiho Pharmaceutical, TP Therapeutics, Foundation Medicine, Natera, and Guardant and has received research funding from Pfizer, Novartis, and Roche/Genentech. The remaining authors declare no conflict of interest.

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ISSN: 1556-0864
https://doi.org/10.1016/j.jtho.2018.09.001

Keywords: Immunotherapy; Immune checkpoint inhibitor; Tyrosine kinase inhibitor; Crizotinib; Hepatotoxicity; Non–small cell lung cancer

Introduction

Immune checkpoint inhibitors (ICIs) targeting programmed cell death 1 and its ligand programmed death ligand 1 (PD-L1) have entered the clinic across multiple solid tumors, including NSCLC.[1] On the basis of KEYNOTE-189, pembrolizumab plus platinum-doublet chemotherapy is the standard first-line treatment for nonsquamous NSCLC lacking *EGFR* mutation or ALK receptor tyrosine kinase gene (*ALK*) rearrangement regardless of PD-L1 status,[2] and pembrolizumab alone represents an additional first-line option for NSCLC with a high level of PD-L1.[3] In the clinic, PD-L1 results may return faster than other genetic testing results (e.g., *EGFR*, *ALK*, *ROS1*, and *BRAF* alterations), or tissue may be insufficient for genotyping, prompting the initiation of an ICI before genotype-directed tyrosine kinase inhibitors (TKIs).

Thus far, insights into the potential toxicities of sequential ICI and TKI therapy have been limited. In one observational study, the risk of EGFR TKI–associated pneumonitis was substantially higher with sequential or concurrent ICI and TKI therapy, although other toxicities were not investigated.[4] In a separate phase II study of pembrolizumab in TKI-naive *EGFR*-mutant NSCLC, two of seven patients subsequently treated with an EGFR TKI experienced grade 3 transaminitis and grade 5 pneumonitis, respectively, similarly raising concerns of increased risks with sequential administration of ICIs and TKIs.[5] Notably, a high incidence of hepatotoxicity has been reported with certain strategies of concurrent ICI and TKI administration in NSCLC.[6-8] For example, a phase 1/2 study of nivolumab plus crizotinib in *ALK*-rearranged NSCLC was terminated early because of severe hepatotoxicity in five of 13 patients (38%).[6] Two patients died, highlighting the importance of diagnosing and intervening on potentially fatal hepatotoxicity. To our knowledge, no study has evaluated whether the use of an ICI followed by TKI is associated with an increased risk of hepatotoxicity. ICIs and TKIs individually can cause hepatotoxicity, and ICIs have long half-lives that could affect the development of subsequent TKI-associated hepatotoxicity.

Crizotinib is a multitargeted ALK receptor tyrosine kinase/ROS1/MET proto-oncogene, receptor tyrosine kinase (MET) inhibitor, which remains the only approved, standard first-line therapy for *ROS1*-rearranged NSCLC.[9] It also represents a clinically meaningful treatment option for NSCLC harboring MET alterations, and recently received U.S. Food and Drug Administration breakthrough therapy designation for NSCLC with *MET* exon 14 skipping.[10] Here, we report on a retrospective study of 453 patients with *ALK*/*ROS1*/*MET*-altered advanced NSCLC who received crizotinib with or without prior ICI therapy, designed to address whether sequential ICI and crizotinib use increases the risk of hepatotoxicity.

Methods

We identified patients with advanced NSCLC who harbored an *ALK* fusion, *ROS1* fusion, or *MET* exon 14 skipping or amplification who were treated at Massachusetts General Hospital between January 2008 and April 2018. Sequential treatment with an ICI followed by crizotinib was required. For the comparator, we identified patients treated with crizotinib only. Hepatotoxicity occurring during crizotinib treatment was annotated and graded per the Common Terminology Criteria for Adverse Events, version 4.0. All data were updated as of April 1, 2018. Records were reviewed under an institutional review board–approved protocol.

Categorical and continuous variables between groups were compared by using the Fisher exact test and Wilcoxon rank-sum test, respectively. The cumulative incidence of hepatotoxicity was estimated from the start of crizotinib therapy to the onset of grade 3 or 4 transaminitis and compared between groups by using the Gray test. Among patients treated with crizotinib who did not experience hepatotoxicity, the date of discontinuation of crizotinib therapy was analyzed as a competing risk or censored on the last follow-up date if continuing on crizotinib at the time of data analysis. Statistical analysis was performed with Stata software (version 14, Stata Corp LP, College Station, TX) and SAS software (version 9.4, SAS Institute Inc., Cary, NC), with p values based on a two-sided hypothesis.

Results

We identified 453 patients with ALK-driven (n = 345), ROS1-driven (n = 83), or MET-driven (n = 25) NSCLC. Eleven patients received an ICI before receiving crizotinib, and 442 received crizotinib only (Supplementary Table 1). Baseline patient characteristics between the sequential ICI-crizotinib cohort and the crizotinib-only cohort were comparable overall; however, more patients in the sequential ICI-crizotinib cohort had MET-driven NSCLC and a history of smoking (see Supplementary Table 1). There was no difference between the cohorts in terms of the presence of liver conditions (none of 11 patients [0%] versus 16 of 442 [4%] [$p > 0.999$]) or hepatic metastases before administration of crizotinib (two of 11 patients [18%] versus 101 of 442 [23%] [$p > 0.999$]) (see Supplementary Table 1).

Table 1. Detailed Characteristics of Patients Who Received Crizotinib after an ICI (n = 11)

ID	ICI	TKI	Oncogenic Driver	ICI Line	ICI Doses, n	ICI-CRZ Interval, d	Liver Metastasis	PD-L1 TPS	PD-L1 Ab	ALT/AST Increase	CRZ-Liver Tox Interval, d	Liver Tox Duration, d	CRZ Interruption
1	Pembrolizumab + chemotherapy	Crizotinib	ALK	1	3	23	No	95%	22C3	Gr 4 ALT Gr 4 AST	38	37	Drug discontinued
2	Pembrolizumab + chemotherapy	Crizotinib	*ALK*	1	1	21	No	70%	22C3	Gr 4 ALT Gr 4 AST	27	44	Drug discontinued
6	Pembrolizumab	Crizotinib	*ALK*	1	1	10	No	60%	E1L3N	No	N/A	N/A	N/A
7	Pembrolizumab	Crizotinib	*ROS1*	2	3	27	No	20%	E1L3N	No	N/A	N/A	N/A
8	Nivolumab + ipilimumab	Crizotinib	*ROS1*	1	2	121	No	<1%	E1L3N	No	N/A	N/A	N/A
9	Atezolizumab + investigational drug	Crizotinib	*ROS1*	3	2	25	Yes	N/A	N/A	No	N/A	N/A	N/A
10	Nivolumab	Crizotinib	*MET* amp	2	12	73	No	0%	E1L3N	Gr 1 ALT Gr 1 AST	27	140	Dosing not interrupted
3	Nivolumab	Crizotinib	*MET* amp	2	4	30	Yes	50%	E1L3N	Gr 4 ALT Gr 4 AST	42	98	Drug discontinued
4[a]	Nivolumab	Capmatinib → crizotinib + ibrutinib	*MET* ex 14	1	9	135	No	0%	E1L3N	Gr 3 ALT Gr 3 AST	49	61	Drug discontinued
5	Pembrolizumab	Crizotinib	*MET* ex 14	1	7	42	No	>90%	E1L3N	Gr 3 ALT Gr 2 AST	13	15	Held for 36 d; resumed with dose reduction
11	Pembrolizumab	Crizotinib	*MET* ex 14	3	2	99	No	95%	E1L3N	No	N/A	N/A	N/A

Note: ICI Line refers to the line of systemic therapy for ICI; ICI Doses refers to the number of ICI doses received by the patient. ICI-CRZ Interval refers to the time interval between the last dose of ICI and the start of crizotinib therapy. Liver Metastasis refers to the presence of liver metastases before the patient started taking crizotinib. CRZ-Liver Tox Interval refers to the interval between the start of crizotinib therapy and onset of liver toxicity. Gr refers to grade per the Common Terminology Criteria for Adverse Events, version 4.0.

[a]The patient received nivolumab, which was followed initially by capmatinib. Soon thereafter, chronic lymphocytic leukemia was diagnosed, requiring discontinuation of capmatinib. The patient subsequently received crizotinib (for lung cancer) combined with ibrutinib (for chronic lymphocytic leukemia). The increase in ALT/AST level was attributable to crizotinib (the levels improved when crizotinib was withheld and recurred with rechallenge of crizotinib).

ID, identifier; ICI, immune checkpoint inhibitor, TKI, tyrosine kinase inhibitor; CRZ, crizotinib; PD-L1, programmed death ligand 1; TPS, tumor proportion score; Ab, antibody; ALT, alanine transaminase; AST, aspartate transaminase; Tox, toxicity; *ALK*, ALK receptor tyrosine kinase gene; Gr, grade; *MET*, MET proto-oncogene, receptor tyrosine kinase gene; amp, amplification; N/A, not applicable; ex 14, exon 14 skipping.

Five of the 11 patients receiving sequential ICI and crizotinib experienced development of a grade 3/4 increase in alanine transaminase (ALT) level (cumulative incidence 45.5% [95% confidence interval (CI): 14.9–72.2]), three cases of which (27.3%) were grade 4. In comparison, 34 of the 442 patients treated with crizotinib only (8.1% [95% CI: 5.4–10.5, $p < 0.0001$]) experienced development of a grade 3/4 increase in ALT level, four cases of which (0.9%) were grade 4. A grade 3/4 increase in aspartate transaminase level occurred in four of the 11 patients who were receiving sequential ICI and crizotinib therapy (cumulative incidence 36.4% [95% CI: 10.0–64.2]) versus in 14 of the 442 who were receiving crizotinib only (3.4% [95% CI: 1.9–5.5, $p < 0.0001$]) (Table 2). Grade 5 hepatotoxicity was not observed in either cohort. The median interval between initiation of crizotinib therapy and onset of grade 3 or higher transaminitis was 38 days (range 13–49) versus 41 days (range 5–1657) for patients receiving sequential ICI-crizotinib and crizotinib only, respectively. The median interval between the last ICI dose and initiation of crizotinib was 30 days (range 21–135) among the patients in the sequential ICI-crizotinib cohort who experienced development of a grade 3/4 increase in transaminase level versus 50 days (range 10–121) among those who did not.

Of note, none of the five patients who received sequential ICI and crizotinib and developed grade 3 or higher transaminitis had preexisting autoimmune or liver conditions. One (patient 3 [see Table 1]) had hepatic metastases with baseline grade 1 transaminitis; all the others had normal baseline transaminase levels. Four had received an ICI as first-line therapy (see Table 1). For patients 1, 2, and 5, a high PD-L1 tumor proportion score (>50%) was returned earlier than the results of *ALK/ROS1/MET* testing, prompting initiation of an ICI (see Table 1). Patient 4 had recurrence of NSCLC shortly after completing adjuvant chemotherapy and began taking nivolumab before any *MET* testing results had been received.

The duration of hepatotoxicity in these five patients ranged between 15 and 98 days (median 44 days). Four had a concurrent grade 1 increase in bilirubin level, and three had a grade 3 increase in alkaline phosphatase level (see Table 1). No case met the Hy's law criteria. Four patients required permanent discontinuation of crizotinib therapy; one was able to resume taking crizotinib with a dose reduction after it had been held for 5 weeks. All cases were reversible; none required steroids, and liver biopsies were not performed. There was no concomitant pneumonitis.

Discussion

Programmed death 1/PD-L1 inhibitors have become viable treatment options in addition to genotype-directed TKIs in oncogene-driven NSCLC. As a growing number of ICIs gain approval for use in NSCLC, patients are increasingly likely to receive ICI therapy during their disease course. Although the toxicity profiles of TKIs are well established, little is known regarding the potential toxicities of TKIs administered after ICIs.

In this study, we observed a higher incidence of hepatotoxicity with sequential ICI and crizotinib use compared with crizotinib alone. The actuarial rates of grade 3/4 increases in ALT and aspartate transaminase levels with sequential therapy were 45.5% and 36.4%, respectively, versus 8.1% and 3.4% with crizotinib alone (which is consistent with the rates of 3% to 10% that have been reported in trials[11–13]). Therefore, prior

Table 2. Increase in ALT/AST Level with Crizotinib after an ICI versus with Crizotinib Alone

	Patients, n		Cumulative Incidence of Liver Toxicity		
Increase in ALT/AST Level	Total	Liver Toxicity	Point Estimate, %	(95% CI)	*p* Value
Grade 3/4 increase in ALT level					<0.0001
ICI → TKI	11	5	45.5	(14.9-72.2)	
TKI	442	34	8.1	(5.7-11.0)	
Grade 4 increase in ALT level					<0.0001
ICI → TKI	11	3	27.3	(5.8-55.4)	
TKI	442	4	0.9	(0.3-2.2)	
Grade 3/4 increase in AST level					<0.0001
ICI → TKI	11	4	36.4	(10.0-64.2)	
TKI	442	14	3.4	(1.9-5.5)	
Grade 4 increase in AST level					<0.0001
ICI → TKI	11	3	27.3	(5.8-55.4)	
TKI	442	1	0.2	(0.02-1.3)	

Note: Grading is per the Common Terminology Criteria for Adverse Events, version 4.0.
Point estimate is reported at the time of last observed event.
ALT, alanine transaminase; AST, aspartate transaminase; TKI, tyrosine kinase inhibitor; ICI, immune checkpoint inhibitor; CI, confidence interval.

exposure to an ICI may significantly increase the risk of crizotinib-associated hepatotoxicity. Although increased toxicities, including transaminitis, were observed in early-phase studies evaluating concurrent administration of nivolumab plus crizotinib (CheckMate 370)[6] and avelumab plus crizotinib (JAVELIN Lung 101),[14] this is the first study to our knowledge to evaluate the effect of sequential ICI and TKI therapy on the risk of hepatotoxicity.

Our findings suggest that patients with ROS1/MET/ALK-driven NSCLC who receive crizotinib after an ICI need to be cautioned and closely monitored for the development of hepatotoxicity. Of note, alectinib rather than crizotinib is now the standard first-line therapy in *ALK*-rearranged NSCLC, and the clinical impact of sequential ICI and alectinib was not evaluated in this study. It is worth noting, however, that in a phase Ib trial of concurrent administration of alectinib and atezolizumab in *ALK*-rearranged NSCLC, an acceptable safety profile was observed, with a grade 3 increase in ALT level occurring in two of 21 patients (9.5%).[15] These findings are in line with the acceptable tolerability of concurrent administration of lorlatinib and avelumab,[14] yet they are in contrast to the increased hepatotoxicity of crizotinib plus avelumab,[14] crizotinib plus nivolumab,[6] and ceritinib plus nivolumab.[8] Indeed, the tolerability of different sequential or concurrent ICI-TKI strategies may be TKI specific, urging further studies to elucidate which combinations or sequences of an ICI and a TKI may be safe and viable options for patients. As suggested by the increased hepatotoxicity seen with an ICI plus crizotinib or ceritinib—versus with alectinib or lorlatinib—the baseline level of hepatotoxicity seen with each TKI may affect the development of increased hepatotoxicity when it is used with an ICI in a concurrent or sequential approach.

Our study had several noteworthy limitations. It was a retrospective study subject to inherent selection biases and potential confounding by unmeasured risk factors. Further, the number of patients who received sequential ICI and crizotinib therapy was small. Of note, although a higher proportion of those in the sequential ICI-crizotinib cohort had *MET* alterations and were smokers (possibly reflecting the association with *MET* alterations[10]) than in the crizotinib-only cohort (see Supplementary Table 1), the rate of hepatotoxicity is not known to be different in patients with *MET*-altered tumors.[10] Additionally, it was not feasible to evaluate all sequences of available ICIs and TKIs; as we have mentioned, it is likely that toxicities arising from strategies involving sequential or concurrent administration of an ICI and TKI may be TKI specific. Finally, the mechanism by which prior treatment with an ICI may augment the risk of TKI-associated hepatotoxicity remains poorly understood. Further studies will help determine whether prior ICI use may "prime" the immune system toward a TKI-induced inflammatory response.

In conclusion, prior immunotherapy may significantly increase the risk of crizotinib-associated hepatotoxicity. Careful monitoring for hepatotoxicity is therefore recommended in patients treated sequentially with an ICI and crizotinib. In parallel, further studies are needed to define the safety profile of different sequences of ICIs and TKIs and identify feasible treatment strategies in oncogene-driven NSCLC. Until a more fine-tuned understanding of specific ICI-TKI sequences is available, caution may be advised when clinicians face the real-world question of whether to utilize immunotherapy in patients with oncogene-driven NSCLC who may still have TKI options. In patients newly diagnosed with advanced-stage NSCLC, baseline comprehensive genotyping to identify targetable driver oncogenes should be expedited, and the corresponding results should be incorporated along with the PD-L1 status to optimally inform treatment stratification and minimize potentially preventable toxicities.

Acknowledgments

This work was supported by a grant from the National Cancer Institute (R01CA164273 [to Dr. Shaw]), by Be a Piece of the Solution, and by the Targeting a Cure for Lung Cancer Research Fund at Massachusetts General Hospital.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2018.09.001.

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