Previous/Concurrent Radiation Enhanced the Efficacy of Immunotherapy in Metastatic and Recurrent Liver Cancer: A Pilot Study from the Real-world Data

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OBJECTIVE

Liver cancer is one of the leading causes of cancer-related death globally, with hepatocellular carcinoma (HCC) the most common histological type. Surgery, liver transplantation and radiofrequency ablation are helpful for patients with early stage. However, the prognosis is disappointing for patients with metastatic and recurrent disease, despite standard therapeutic regimen sorafenib or lenvatinib. Therefore, there remains a great necessary for novel multimodality treatment strategies for this subgroup of patients.

Immunotherapy, especially programed cell death checkpoint inhibitors(anti-PD1) is emerged as an efficient treatment in various of carcinomas. Recently, several studies tried to deliver anti-PD1 regimens to metastatic HCC patients. Nevertheless, the result is controversial. Researches concerning on other malignancies, such as lung cancer showed encouraging survivals after the combination of radiation and anti-PD1 drugs based on the fact that preclinical studies have pointed that radiation also induced systemic response by activating CD8+ T-cells. Meanwhile, more and more evidence identified the efficacy of radiotherapy in HCC. It is reasonable to use radiation combined with anti-PD1 to increase its response rate as well as furtherly improve treatment outcomes.

This pilot study was conducted to investigate the efficacy and safety of the combination of radiation and PD-1 inhibitors in metastatic and recurrent liver cancer, especially HCC.

METHODS

Trial protocol approval was given by the institutional ethics committee of Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China.

Patients diagnosed with stage IV (American Joint Committee on Cancer Staging System 8th) or recurrent HCC, with Eastern Cooperative Oncology Group performance score 0-2 points and aged 18-75 years old would be evaluated by multi-disciplinary team. Usually, multimodality therapy would be delivered. After that, patients who received radiotherapy followed by PD-1 inhibitors or concurrent radiation and PD-1 inhibitors were enrolled. Data regarding clinicopathologic characteristics, treatment details, serum alpha fetoproteins , response rates, toxicities in different periods, and survivals were collected. Survivals were calculated from the first delivery of immunotherapy using Kaplan-Meier method. Toxicities were evaluated according to National Cancer Institute Common Toxicity Criteria of Adverse Events, version 4.0.

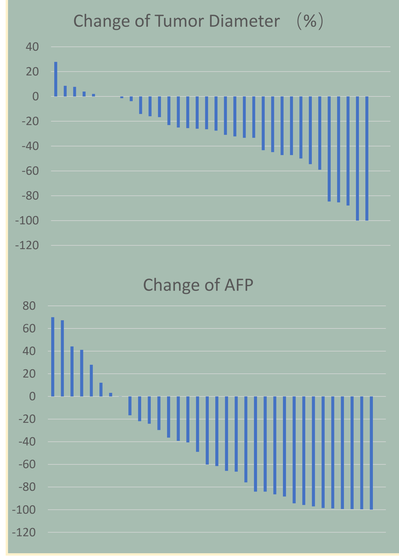
RESULTS

From April 2017 to December 2020, 34 patients were eligible. Twenty-nine (85.3%) patients were male and 5(14.7%) were female. The median age was 58 years old. Thirty-one patients (91.2%) had hepatocellular carcinoma. Totally, radiotherapy was delivered to 92 lesions (28 liver, 28 venous tumor emboli, 13 lymph nodes, 18 bone, 5 others) of these patients. The radiation dose ranged from 40Gy to 60Gy (2-5Gy per fraction). Fifteen patients, 16 patients , 5 patients, 1 patient and 1 patient received sintilimab, toripalimab, camrelizumab, nivolumab and pembrolizumab, respectively. PD-1 inhibitors were administered very 3 weeks until progression or limiting toxicities. Thirty-one patients received targeted therapy during the utilization of immunotherapy and radiotherapy, including 17 patients with sorafenib, 10 patients with lenvatinib, 3 patients with regorafenib and 1 patient with apatinib. After treatment, 3,18 and 11 patients achieved complete response, partial response and stable disease. The response rate and disease control rate were 61.8% and 94.1%, respectively. Grade 3 adverse events were observed in 11 patients (32.3%), including 6 patients with thrombocytopenia (2 with Grade 4, 4 with Grade 3), 2 patients with gastrointestinal events and 3 with others. No grade 5 adverse event was recorded. The median follow up time was 16.5 months. The median overall survival (OS) time and progression free survival (PFS) time were 15.4 months and 11.3 months. One-year OS and PFS were 62.9% and 46.5%, respectively. Two-year OS and PFS were 31.8% and 11.3%, respectively.

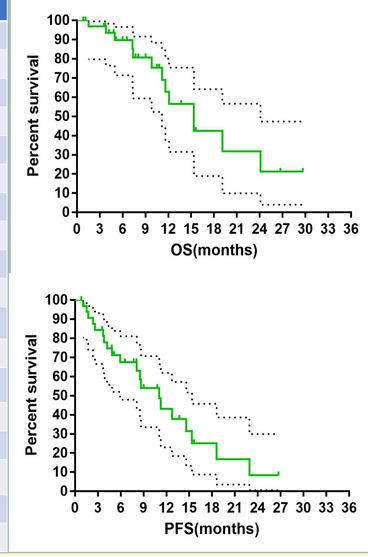
CHARACTERRISTICS&TREATMENTS

	N	%		N	%		N	%		N	%		N	%
Gender			**Child-pugh**			**TNM Stage**			**Immunotherapy**			**RT**		
Male	29	85.3	A	33	97.1	**Primary**			Toripalimab	14	41.2	IMRT	29	85.3
Female	5	14.7	B	1	2.9	IIIC	3	8.8	Sintilimab	12	38.2	VMAT	2	2.9
Age	58y (36-74y)		**Liver cirrhosis**			IVA	3	8.8	Camrelizumab	2	5.9	TOMO	2	2.9
Alcohol			Yes	18	52.9	IVB	5	14.7	Pembrolizumab	1	2.9	**Target**		
Yes	17	50.0	No	16	47.1	**Recurrent**			Nivolumab	1	2.9	Sora	17	50.0
No	17	50.0	**Pathology**			I	2	5.9	Multidrug history	4	11.8	Lenva	10	29.4
Hepatitis			HCC	31	91.2	II	2	5.9	**Combination**			Rego	3	8.8
HBV	27	79.4	Mixed	1	2.9	IIIA	3	8.8	Concurrent	12		Apa	1	2.9
HCV	2	5.9	Cholangiocarcinoma	2	5.9	IIIB	4	11.8	Sequential	22		RT=radiotherapy Sora=sorafinib Lenva=lenvatinib, Rego=regorafenib Apa=apatinib.		
No	5	14.7	**Barcelona Stage**			IIIC	1	2.9	**RT dose**					
ECOG			A-B	5	14.7	IVA	1	2.9	EQD2 (Gy)	56				
1	34	100	C	29	85.3	IVB	1	2.9	range	47-63				

RESPONSE, AEs & SURVIVALS



AE	N	%	AE	N	%
GI			**Skin**		
G1	3	8.8	G1	2	5.9
G2	2	5.9	G2	1	2.9
G3	3	8.8	G3	1	2.9
ALT			**WBC**		
G1	8	23.5	G1	12	35.3
G2	5	14.7	G2	4	11.8
AST			G3	2	5.9
G1	9	26.5	Hb		
G2	8	23.5	G1	3	8.8
Cardio			PLT		
G3	1	2.9	G1	5	14.7
Thyroid			G2	2	5.9
G1	5	14.7	G3	4	11.8
G2	1	2.9	G4	1	2.9
Renal					
G1	1	2.9			
G2	1	2.9			



CONCLUSION

The combination of immunotherapy and radiotherapy was safe and tolerable. The application of radiation before or during PD-1 inhibitors delivery fostered the immune response and enhance the efficacy of immunotherapy with favorable PFS and OS in recurrent and metastatic liver cancer. A Phase II prospective with large number of patients is ongoing.