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Comment

Combinational Treatments Must Follow the Principle of Drug Combination-Feeling from the Treatments of Hepatocellular Carcinoma

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Treatments for liver cancer have been generally divided into liver-directed and systemic therapies. Systemic treatments include chemotherapy, molecular targeted therapy, and immunotherapy. In the recent one decade, the treatment using targeted drugs for Hepatocellular Carcinoma (HCC) has been aggressive, such as Sorafenib as a hallmark [1-2], followed by Lenvatinib as the first-line treatment [3]. Regorafenib is recommended as the second-line therapy [4]. Trials with immunotherapy including anti-PD1 or anti-PD-L1 antibodies are ongoing. Although KEYNOTE-224 and KEYNOTE-240 failed to achieve positive results, overall survival of patients with checkpoint inhibitor seems better than the control group [5-6]. The effect of chemotherapy on HCC is still controversial for advanced HCC [7]. Despite the breakthroughs in drug therapy for HCC, it remains a systematic treatment but not a radical cure, with such a palliation to prolong the survival for a few months. It is mandated to explore more effective combination of novel drugs with other treatment modalities.

The use of combinational anti-cancer treatments for HCC should follow these principles: Firstly, the use of anti-cancer drugs alone is partially effective. Secondly, the combined use of a drug and other treatment modalities should be selected based on toxicity that does not overlap each other. Thirdly, different mechanisms of action with the combined treatments should be considered. We reviewed www.clinicaltrials.gov which is a database of privately and publicly funded clinical studies conducted around the world. The screening of the disease HCC included 1773 studies and consisted of 230 phase 3 studies. Among them, 65 studies were completed and 11 studies had available results. We selected the studies using anti-cancer drug combined with other treatment modalities, and 6 studies met the condition as listed in (Table 1). Unfortunately, all these clinical trials using combinational treatments including anti-cancer drug had either no results or negative results. We also reviewed 2019 ASCO annual meeting abstracts with phase 1 or 2 clinical trials on HCC testing combined anti-cancer drugs, as listed in Table 1. However, most of the trials presented with grade 3 or higher treatment-related adverse events ranged from 53% to 85%, with the toxicity beyond permissible limits (usually less than 35%). These combination therapies failed to follow the principle of drug combination, which was the main reason for the negative results. Some trials used the combinational therapy with the drugs such as Erlotinib, Avelumab, or Axitinib, which had been confirmed with no effect in HCC. Other

Table 1: HCC clinical trials with combined anti-cancer drugs and other treatments in both clinicaltrial.gov and 2019 ASCO abstracts.

Phase 3 clinical trial on HCC using anti-cancer drug combination with other treatment modalities					
NCT No.	**Treatment groups**	**n**	**results**	**P value**	**TRAEs**
617981	Thermo Dox+RFA	354	mTTP:13.9		
	GS+RFA	347	mTTP:13.8		
1829035	Sorafenib	169	mOS:10.8	0.29	
	Sorafenib + TACE	170	mOS:12.8		
149565	resection	135	5y RFS:48.6	0.828	
	Resection+IFNα-2b	135	5y RFS:42.2		
494299	TACE+Sorafenib	229	TTP:5.4	0.252	
	TACE+Placebo	229	TTP:3.7		
901901	Sorafenib+ Erlotinib	362	mOS:9.5	0.2	
	Sorafenib+Placebo	358	mOS:8.5		
692770	Resection+Sorafenib	556	mRFS:33.3	0.26	
	Resection+Placebo	558	mRFS:33.7		
Studies on HCC testing combined anti-cancer drugs from 2019 ASCO annual meeting					
ASCO abstract No.	**Treatment groups**	**n**	**results**	**P value**	**TRAEs**
4012	Nivo 1+Ipilimu 3 Q3w×4	50	mOS 22.8m		III-IV 53%
	Nivo 3+Ipi 1 Q3w×4	49	mOS 12.5m		29%
	Nivo 3 Q2w/Ipi 1 Q6w	49	mOS 12.7m		31%
e15630	Sorafenib+oxaliplatin+capecitabine	22	TTP: 3.2:2.8m,	0.29	
	Sorafenib alone	24			
TPS4152	Lenvatinib + pembro	30	mOS: 14.6m		
	Lenvatinib+Placebo		ORR: 26.9%		
			(Keynote 524)		
4074	Camrelizumab +FOLFOX/GEMOX	34	ORR: 9(26.5)		III-IV 85.3%
4072	Avelumab+ Axitinib	22	1-year OS 54.5% ORR:13.6%		III 72.7%
e15601	TACE+Sorafenib	73	mOS:17.2:12.1m;	0.024	
	TACE only	60			
	TACE+Sorafenib	55	mOS:42.7:32.6m;	0.247	
	TACE only	72			

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trials combined more than one systemic therapy, but the toxicity of individual drug (molecular targeted drugs and/or checkpoint inhibitors) overlapped with each other. Surprisingly, a lot of phase 1 or 2 clinical trials were investigating the combinational systemic therapies, but none of them followed the principles of combination treatment. Fortunately, PACIFIC study was the most successful clinical trial on the combination therapies for non-small cell lung cancer. It did follow the three principles of combined therapies, including effective drug choice when used alone, space-time synergy, and no overlapped toxicity.

Lastly, it is very important to select the right beneficiaries in cancer treatment. Anti-cancer drugs are sometimes effective for a specific group of patients. The beneficiaries of systemic therapy are often patients with the intermediate or advanced stages. Early-stage patients receive systematic treatment with less likely benefit. Principal Investigators of clinical trials need the interdisciplinary collaboration to face the challenges of combinational treatments, and maintain a balance between the principles and the drug preference of the industry to obtain the maximum benefits.

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