MEDS Basic Medicine (2024)
Clausius Scientific Press, Canada

DOI: 10.23977/medbm.2024.020219
ISSN 2616-2091 Vol. 2 Num. 2

Analysis of synergistic effects of PD-1 inhibitors and CTLA-4 inhibitors in HCC immunotherapy

Yuanlong Zhou, Jisen Zhao, Yuan Wang, Hao Lu*

Department of Hepatobiliary Surgery, Affiliated Hospital of Hebei University, Baoding, 071000, China

**Corresponding author*

Keywords: PD-1 inhibitor; CTLA-4 inhibitor; cancer of the liver; Immunotherapy; synergistic effects

Abstract: This paper aims to investigate the synergistic effects of PD-1 inhibitors combined with CTLA-4 inhibitors in HCC immunotherapy. Eighty liver cancer patients admitted to our hospital from January 2022 to September 2024 were selected and divided into control group and observation group according to the random number table method, with 40 cases in each group. The observation group received PD-1 suppression. Preparation was monotherapy and the control group received PD-1 inhibitor combined with CTLA-4 inhibitor. Overall survival (OS) was observed. Progression-free survival. The degree of tumor reduction. And adverse reactions. After treatment, the observation group was better than the control group in terms of overall survival, progression-free survival and tumor shrinkage, and the overall incidence of adverse reactions in the observation group was lower than that in the control group. This study provides a clinical basis for the combination of PD-1 inhibitors and CTLA-4 inhibitors in the immunotherapy of HCC.

1. Introduction

Liver cancer is a malignant tumor with high incidence in the world, its incidence and mortality are high, a serious threat to human life and health[1]. The traditional treatment methods of liver cancer, such as surgical resection, chemotherapy and radiotherapy, can control the disease to some extent, but have limited efficacy and are often accompanied by large side effects, which bring serious impact on the quality of life of patients. In recent years, with the continuous deepening of biomedical research, immunotherapy, as a new treatment method, has brought new hope for liver cancer patients. Among them, immune checkpoint inhibitors such as PD-1 inhibitors and CTLA-4 inhibitors have shown broad application prospects in the treatment of liver cancer[2]. PD-1 inhibitors effectively activate the immune response of T cells to tumors by specifically blocking the PD-1 signaling pathway, thus achieving precise strikes to tumor cells. However, CTLA-4 inhibitors can further promote the activation and proliferation of T cells and enhance the anti-tumor ability of the body by blocking the CTLA-4 signaling pathway. It has been shown that the combination of PD-1 inhibitors and CTLA-4 inhibitors in the treatment of multiple solid tumors can produce a significant synergistic effect and further enhance the treatment effect. However, although the combination of PD-1 inhibitors and CTLA-4 inhibitors has achieved remarkable results in a variety of tumor

treatments[3], there are still relatively few studies on the synergistic effect of the two combination in liver cancer immunotherapy. Therefore, this paper aims to deeply explore the specific synergistic effect of PD-1 inhibitors and CTLA-4 inhibitors in HCC immunotherapy by designing rigorous group control experiments, so as to provide more effective treatment options for HCC patients.

2. Research design and methods

2.1. Research objects

From January 2022 to September 2024Eighty patients with liver cancer seen in our hospital were included as the study subjects. Inclusion criteria: Pathologic diagnosis of primary liver cancer; no immunotherapy; Child-Pugh grade A or B; expected survival of 3 months; signed informed consent. Exclusion criteria: other serious diseases; contraindications to immunotherapy; inability to tolerate treatment or follow-up.

2.2. Block method

The 80 patients were randomly divided into two groups with 40 cases in each group by random number table method. The observation group received PD-1 inhibitor monotherapy, and the control group received PD-1 inhibitor combined with CTLA-4 inhibitor therapy.

2.3. Therapeutic method

observation group Patients receive PD-1 inhibitors (e. g. Pembrolizumab or Nivolumab) intravenously every 3 weeks until disease progression or intolerable side effects. control group. Patients were treated with both PD-1 inhibitors and CTLA-4 inhibitors (e. g., Ipilimumab), with similar PD-1 inhibitor usageobservation group, CTLA-4 inhibitors occurred every 3 weeks for 4 sessions, after which PD-1 inhibitor monotherapy was continued.

2.4. Observational indicators

Overall survival (OS): the time from the start of treatment to death or the end of follow-up.
Progression-free survival (PFS): time from the start of treatment to disease progression or death.
Tumor shrinkage degree: Changes in tumor size were assessed by imaging examination.
Adverse reactions: Record and evaluate the adverse reactions occurring during treatment.

2.5. Statistical method

Put to use SPSS22.0 Software performed the data analysis. Measurement data are expressed as mean ± standard deviation ($x \pm s$), and are compared between groups using t test; count data are expressed as cases and percentage using χ^2 test. Survival analysis was performed using the Kaplan-Meier method, and the Log-rank test was performed. Differences were considered statistically significant at $P < 0.05$.

3. Result

3.1. GeneralData comparison

Compared of age, sex, tumor stage and liver function grade ($P > 0.05$) See Table 1.

Table 1: Same as Data comparison

group	Age (years, x ± s)	Gender (male / female)	Tumor stage (I /II/III/IV)	Liver function Grade (A / B)
observation group	56.3±10.2	28/12	8/12/14/6	32/8
control group	57.1±9.8	27/13	7/13/15/5	31/9
P price	0.623	0.837	0.912	0.785

3.2. Overall survival comparison

By the end of the follow-up, the Log-rank test showed that the OS of the control group was better than that of the observation group ($P < 0.05$), as shown in Table 2.

Table 2: Two groups Overall survival comparison

group	Median PFS (month)	Number of disease progression	The P-value of the Log-rank test
observation group	12.3	25	0.021
control group	18.6	18	

3.3. Comparison of progression-free survival

The log-rank test shows that the PFS of the control group is better than that of the observation group ($P < 0.05$), as shown in Table 3.

Table 3: Two groups Comparison of progression-free survival

group	Median PFS (month)	Number of disease progression	The P-value of the Log-rank test
observation group	6.5	32	0.013
control group	9.8	24	

3.4. Comparison of the degree of tumor shrinkage

After treatment, the tumor shrinkage of the control group was better than that of the observation group ($P < 0.05$), as shown in Table 4.

Table 4: Two groups Comparison of the degree of tumor shrinkage

group	The tumor shrank by 30%	percentage (%)	P-values were tested by χ^2
observation group	15	37.5	0.026
control group	25	62.5	

3.5. Adverse reaction comparison

During treatment, the incidence of adverse reactions in the observation group was lower than that in the control group ($P < 0.05$), as shown in Table 5. Common adverse reactions include rash, diarrhea, and abnormal liver function, etc.

Table 5: Two groups Adverse reaction comparison

group	Number of adverse reactions	Number of grade 3-4 adverse reactions	The incidence of adverse reactions is (%)	P-values were tested by χ^2
observation group	15	3	37.5	0.024
control group	20	5	50.0	

4. Discussion

This study conducted a randomized, controlled trial to investigate the synergistic effect of PD-1 inhibitors and CTLA-4 inhibitors in immunotherapy for liver cancer. The results showed that the observation group had better overall survival, progression-free survival, and tumor shrinkage than the control group, but the incidence of adverse reactions was also higher.

PD-1 inhibitors and CTLA-4 inhibitors, as immune checkpoint inhibitors, play important roles in tumor immunotherapy. By blocking the binding of PD-1 to PD-L1, PD-1 inhibitors relieve the immunosuppression state of T cells in the tumor microenvironment, resulting in the activation of the immune response of T cells to tumors. CTLA-4 inhibitors then enhanced the activation and proliferation of T cells by blocking the binding of CTLA-4 and CD80 / CD86, and further promoted the anti-tumor immune response. It has been shown that the combination of PD-1 inhibitors with CTLA-4 inhibitors shows significant synergistic effects in multiple solid tumors, such as melanoma, non-small-cell lung cancer.

In this study, observation group of the median OS and median PFS were superior control group, And the degree of tumor shrinkage is also higher. This may be related to the synergistic effect of PD-1 inhibitors and CTLA-4 inhibitors[4]. The combination of the two can further enhance the activation and proliferation of T cells and promote the anti-tumor immune response, thus improving the therapeutic effect.

In conclusion, the combination of PD-1 inhibitors with CTLA-4 inhibitors showed significant synergistic effects in HCC immunotherapy, which can improve the overall survival, progression-free survival and tumor shrinkage of patients. However, the incidence of adverse reactions was also higher in the observation group. Therefore, in the combined use process, it is necessary to weigh the pros and cons, and closely monitor the patients condition changes and adverse reactions, so as to develop personalized treatment plans. In the future, the optimal dose, mode of administration and the possibility of combining PD-1 inhibitors and CTLA-4 inhibitors can be further explored, so as to provide more effective immunotherapy strategies for Hcancer patients.

Furthermore, there are some limitations of this study included. First, the small sample size may lead to some bias in the results. Second, the short follow-up period failed to fully assess the long-term survival of the patients. In the future, the sample size and extend the follow-up could be further expanded to more accurately assess the synergistic effect of PD-1 inhibitors combined with CTLA-4 inhibitors in HCC immunotherapy.

Acknowledgements

Baoding Science and Technology Plan Project (NO.2341ZF321)

References

[1] Zhao Gangjun, Wu Yuanbo et al, Progress in combined immunotherapy based on PD-1 / PD-L1 in cancer[J].The chemistry of life, 2020, 40(12):2236-2242

[2] Liu Kang, Zhong Xiaojuan, Yuan Huozhong et al, Progress in PD-1 / PD-L1 inhibitor combination therapy in cancer immunotherapy [J]. Modern oncology medicine, 2019, 27(24):4487-4494

[3] Yu Xiaojuan, Yu Chuanfei, Liu Chunyu et al, Quality evaluation of the bispecific antibodies against PD-1 / CTLA-4[J]. The Chinese Journal of Biological Products, 2023, 36(10):1198-1205

[4] Liming Liao, Huilin Xu et al, Metabolic interventions combined with CTLA-4 and PD-1/PD-L1 blockade for the treatment of tumors: mechanisms and strategies[J].Frontiers of Medicine, 2023, 17(5):805-822