Efficacy of Standardised Treatments Combined with Ubenimex in Patients with Malignant Tumors

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ABSTRACT
Ubenimex is widely used as an immunomodulator in the treatment of leukemia and non-small cell lung cancer to improve the anti-tumor treatment effect. However, there has not been any multicenter randomised controlled trials to study its impact on the prognosis of cancer patients. The authors aimed to conduct a meta-analysis to initially study these issues. Pubmed, Cochrane Library and EMBase were searched. Randomised controlled trials of the effects of ubenimex on the survival rate of malignant tumor patients were included in the meta-analysis. Survival rate ratio (OR) and 95% confidence interval (95% CI) between two groups were used to evaluate the efficacy of ubenimex. Fixed effects models were used for meta-analysis. A total of 1,372 cases (684 in the ubenimex group and 688 in the control group) of five studies were included. Between the ubenimex group and the control group, the 1-year OR was 1.40 (95% CI = 1.06 to 1.85), the 2-year OR was 1.43 (95% CI = 1.08 to 1.89) and the 3-year OR was 1.39 (95% CI = 1.07 to 1.81). Standardised treatments combined with ubenimex may improve the survival rate of patients with malignant tumors.

Key Words: Malignant tumors, Ubenimex, Randomised controlled trials, Meta-analysis.

INTRODUCTION
Malignant tumors are important and serious health concern. In the United States, approximately 4,600 people are diagnosed with malignant tumors each day, and 1,650 people die of malignant tumors each day. After a series of standardised treatments (surgery, chemotherapy, radiotherapy etc.), the recurrence rates of many kinds of malignant tumors remain high. In addition to those treatments, combined with some low-toxic adjunctive agents, to improve patients survival, has also become the goals of many scholars and researchers.

The immune system plays an important role in the body’s own anti-tumor activities, and immunotherapy have been increasingly important in the treatment of malignant tumors. In many malignant tumors fields, patients with a wide degree of CD8+ T cell infiltration are indicated to have a better prognosis. The number of natural killer (NK) cells was positively correlated with the prognosis of liver cancer. Improving the function of these immune cells, may become a new way to improve the survival rate of malignant tumors.

Ubenimex is a CD13 inhibitor that enhances immunity by enhancing T cells’ viability and enhancing NK cells’ lethality. Ubenimex can also directly exert its anti-cancer effect by interfering with tumor cell metabolism. At present, ubenimex is widely used as an adjuvant drug in the treatment of leukemia and non-small cell lung cancer to improve the effects of anti-tumor treatment. There has been no report about any serious side effects of ubenimex. However, whether patients with malignant tumors need to use ubenimex is still controversial, and there are still no multicentre large randomised controlled trials to investigate the relationship between ubenimex and prognosis of patients with malignant tumors. This meta-analysis was aimed to initially study these issues, and provide decision-making reference for clinical practice.

METHODOLOGY
Research retrieval adopted the theme words-joint-free words retrieval method. Search terms included bestatin, ubenimex, (D-Leu)-(R-(R*,S*))-isomer, tumour, tumor, malignant neoplasm, cancer, randomised controlled trial (RCT). Pubmed, Cochrane library, and EMBase were searched to collect RCTs about the effects of ubenimex on the survival rate of malignant tumor patients from the establishment of the databases to January 2019.

The inclusion criteria were a randomised controlled trial (RCT); participants must be diagnosed as malignant tumor patients pathologically, regardless of the type of tumor; the control group consisted of patients who received only stan-
The intractability of malignant tumors is a worldwide problem. Although there are many kinds of treatments for malignant tumors; still, no malignant tumor could be claimed to be cured completely. Any method that can improve the survival rate of cancer patients is worth this effort. In the previous study, it was mentioned that metformin significantly improved the prognosis of oral cancer patients with type 2 diabetes mellitus. At the same time, ubenimex, as a low toxicity immunomodulator and as an anticancer drug, has been used in clinic for decades. In vitro experiment, ubenimex induces the autophagic cell death in prostate cancer cells and renal cancer cells. It can also enhance the effects of anticancer drugs in hepatocellular cancer. Compared to in-vitro experiments, there are only a few clinical trials on the anti-tumor effect of ubenimex. In the routine treatment of malignant tumors, whether the use of ubenimex can improve the survival rate of patients, becomes a clinical problem to be solved.

This meta-analysis included a total of five RCT studies. The results (Figure 3 and Figure 4) show that ubenimex may improve the 1-year, 2-year, and 3-year-survival rates of patients with malignant tumors. With the development of high-throughput sequencing technology, human research on cancer has entered the information age. Tumour-infiltrating immune cell has been found playing an increasing important role regarding the anti- or pro-tumorigenesis and prognosis of tumor patients. The immune checkpoint blockade and chimeric antigen receptor T-cell therapies have achieved amazing success. Yamazaki et al. found that natural killer and lymphokine activated killer cell activity of patients with hematological malignancies was significantly lower than normal people, and ubenimex administration can not only elevate the activity of natural killer and lymphokine activated killer cell, but also increase the absolute numbers of helper T-cells, cytotoxic T-cells and natural killer cells. Ubenimex treatment could enhance the susceptibility of gastric cancer cell to lymphokine-activated killer cells. Natural killer cell, B-cell, CD8⁺ T-cell, and active CD4⁺ memory T-cell were found to be survival-favourable immune cells in breast cancer. Thus, ubenimex may improve the tumor immune microenvironment to enhance the clinical therapeutic effect on tumor. Ubenimex may improve the survival rate of patients with malignant tumors by improving the immune system to eliminate more dormant malignant tumor cells.
Efficacy of standardised treatments combined with ubenimex in patients with malignant tumors

Table I: Basic characteristics of included studies.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Published date</th>
<th>Country</th>
<th>Diagnosis of objects</th>
<th>Standardised treatments</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. Mouritzen</td>
<td>1990</td>
<td>Denmark</td>
<td>Stage I and stage II non-small cell lung cancer</td>
<td>Surgery</td>
<td>Ubenimex</td>
</tr>
<tr>
<td>Henric Blomgren</td>
<td>1987</td>
<td>Sweden</td>
<td>Transitional cell carcinoma of the bladder</td>
<td>Radiotherapy</td>
<td>Ubenimex</td>
</tr>
<tr>
<td>M.Takada</td>
<td>1990</td>
<td>Japan</td>
<td>Inoperable lung cancer</td>
<td>Chemotherapy or radiotherapy</td>
<td>Ubenimex</td>
</tr>
<tr>
<td>T. Yasumitsu</td>
<td>1990</td>
<td>Japan</td>
<td>Resected lung cancer</td>
<td>Surgery</td>
<td>Ubenimex</td>
</tr>
<tr>
<td>Yukito Ichinose</td>
<td>2003</td>
<td>Japan</td>
<td>Resected state I squamous-cell lung carcinoma</td>
<td>Chemotherapy or radiotherapy</td>
<td>Ubenimex</td>
</tr>
</tbody>
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Besides the impacts on immune cells, ubenimex has been found to have many direct anticancer effects. Wang et al. found that ubenimex might be a perfect adjunctive therapy for melanoma, when combined with Akt inhibitor. Ubenimex could also induce apoptotic and autophagic cell death through the ROS/ERK pathway. Inoi et al. found that ubenimex played an important role in inhibiting the growth of human choriocarcinoma in nude mice by its direct cytostatic activity.

Survival was the most concerned outcome of the included studies. In the forest plots of Figures 2-4, the results of the five studies were consistent. No significant heterogeneity was found after statistical analysis. However, the limitations of this study still existed including the following aspects: Firstly, as shown in Figure 1, only one selected RCT was blinding of outcome assessment, so detection bias is inevitable. Based on available information, there is no way to judge whether the authors have reported the results selectively; so there may be a certain degree of reporting bias. Secondly, the tumor types are different, and the prognosis of different tumors is different. Thirdly, although the included studies were all RCT studies, the overall number of studies was small, which might cause some bias in the results. Fourthly, despite extensive searches, publication bias cannot be ruled out, such as some grey or missing studies in conference. Finally, the areas and occupations of the patients included in the studies are different, so there may be an inevitable bias in the research results.

CONCLUSION

Ubenimex may improve the survival rate of cancer patients. Clinicians can use ubenimex to improve survival rate based on routine treatment. However, due to the above limitations of the study, the accuracy of the results may be affected. The results also require multiple centres, large numbers of samples, and long-term follow-up randomised double-blind controlled trials to confirm the results.

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CONFLICT OF INTEREST:
The authors declared no conflict of interest.

AUTHORS’ CONTRIBUTION:
XH: Substantial contributions to the conception and design of the work.
HX: Acquisition, analysis of data for the work.
SH: Drafting the work.
TM: Analysis of data.
LY: Acquisition of data.
TS: Final approval of the version to be published; and agreed to be accountable in all respects of the work.

REFERENCES