

Executive Summary

Background

Along recent economical development of Korea, the average life span of the Korean people has been increased dramatically. As the lifespan is increased, average occurrence rate of all cancers have increased from 219.9 cases per 100,000 in 1999 to 252.5 cases per 100,000 in 2005. Even though many reports show different results, it is normally accepted that the occurrence rate of carcinoma of unknown origin (CUP) is 2-6%. However, only 1,500 cases of CUP were reported annually in Korea according to the National Health Insurance records and may hold less significant epidemiologic values. Some experts say that the reason why only a small number of CUP is reported is because the Health Insurance Review Agency's "Drug Guideline for Cancer Patients" does not include CUP. Therefore, when a patient is diagnosed with CUP, the economical burden on the patient is increased dramatically. As of result, many of the CUP patients are being treated under a different diagnosis. This results in underestimating the importance of CUP in the Korean population and inadequate allocation of medical resources. Even though CUP is known to have bad prognosis, various adequate treatments may be performed to increase the patient's survival. It is important to provide an adequate socioeconomic support to apply effective treatment plans for CUP patients. Therefore, systematic reference analysis was performed to evaluate the effects of initial treatment.

Inclusion and exclusion criteria

There was no age limit in selecting CUP studies. The analysis included

both randomized and non randomized clinical studies as well as consecutive case series. All of the CUP patients included in the study failed to detect the cancer origin with abdominal or chest CT/X-ray. Articles that are not original (eg. traditional narrative reviews, letters or editorials), case reports and multiple publications have been eliminated. Also, studies that changes treatment methods during the follow up period has also been eliminated.

Literature search

In order to search the references, MEDLINE, EMBASE, Cochrane Central Register of Controlled Trial(CENTRAL) were used. There were no language limitations and the search date was in between 2009.08.24 to 2009.09.01. KoreaMed, Kiss, Riss4u, KM base were used to search for local publications. The search date was in between 2009.09.08 to 2009.09.09. Since local search engines were not equipped with keyword search functions like in Medline, EMbase and CENTRAL, hand searching was also additionally performed on Korea Cancer Association Publications and The Korean Society for Therapeutic Radiology and Oncology Publications. The selection process was performed by researchers in two groups.

Study selection

Two researchers performed independent review of all references during the initial step. When there were differences in between the two researchers, a third researcher stepped into the process to adjust the differences. The initial selection process was done based on the publication's abstracts and title and the final selection was done after reading the full publication.

Assessment of the Quality

Five evaluation criteria according to the Cochrane review guideline was set for comparative studies. They are sequence generation, allocation concealment, blinding, incomplete outcome data and selective outcome reporting. MINOR instrument was used as an evaluation tool for a single arm studies. Two individual researchers performed the evaluation process and a third researcher confirmed the process.

Data Extraction

A standardized data extraction tool has been used by one clinical researcher and a statistician. The clinical data were reviewed and discussed with the advisory committee, and the survival data collections were reviewed by the statistical principal investigator.

Statistical Analysis

Due to variety of treatment methods and diseases forms, it was unable to combine results from the randomized trials. The median survival rate, one and two year survival rate and response rate have been analysed as common outcomes. For each outcome, we basically combined the results from studies to produce an overall result of the outcome for each treatment subgroup rather than attempting to statistically compare between treatment regimens. Considering heterogeneous clinical characteristics and limitations of study designs of the primary studies due to lack of comparative studies, we performed the analysis in an exploratory approach.

Result

Out of 880 potentially eligible references, total of 34 references based on clinical trials were included in the final analysis. Six publications dealt with comparative treatment studies and 28 publications dealt with single group of chemotherapy therapy regimen. Treatment drugs used, diagnostic criteria and patient characteristics for each included study have been summarized.

The median survival rate of CUP patients was 8.8months when treated with platinum based chemotherapy. One year survival rate was 35% and two year survival rate was 19%. When the patients were divided into cases where taxane which is not currently covered by insurance was used and cases where taxane was used and the results were analyzed, a tendency of improved treatment effects in terms of survival and reactions resulting from the use of taxane was observed in cases where taxane was used (median survival periods; 9.4 vs 8.3 months, one year survival rates; 41 vs 31%, two year survival rates; 22 vs 16% and response rates; 0.39 vs 0.29). The tendency of improvement in survival outcomes when taxane based treatment was given was clearly maintained even when factors that cause heterogeneity between the studies included in the analysis were compensated and statistically significant improvement in median survival periods by around 1.5months($p=0.099$) and one year survival rates by around 8.4%($p=0.023$) could be estimated. The one year survival rate when Taxane and platinum were used in combination was 41.8% and thus it was higher than the case of taxane combination treatment that did not include platinum (36.6%) and the case of platinum combination treatment that did not include taxane (32.11%) and much higher than the case of other combination treatments that did not include taxane nor platinum (25.56%).

Although the treatment that included Platinum showed higher survival outcomes and response rates than cases where Platinum was not included in the results of simple small group analysis (median survival

periods; 9.4 vs 8.3 months, one year survival rates; 41 vs 31%, two year survival rates; 22 vs 16% and response rates; 0.39 vs 0.29), the tendency of these difference was observed to be minor when heterogeneity between studies had been compensated.

Cases where larger numbers of anticancer drugs showed more highly improved outcomes in small ground analysis but the differences were not observed any longer when heterogeneity between studies had been compensated. When cases where new regimens appeared relatively recently were used and cases where traditional regimens were used were reviewed separately, very little differences were shown in survival outcomes.

The response rate was significantly better in groups that used newly developed medicines such as taxane, gemcitabine and irinotecan (29% vs. 38%). Two-drug regimen showed better response rate than single drug regimen and more than triple drug regimen improved the response rate significantly (12% vs. 29% vs. 38%). After correcting differences in histological characteristics, the existence of metastatic tumors in the liver and the patterns of metastasis of patients included in different studies, the above mentioned difference was very small and thus no clear ground appeared for considering that the improvement in response rates contributed to treatment.

Conclusion

Through the results of this study that has been conducted with exploratory based on small group analysis, clear superiority or inferiority between certain treatments could not be confirmed. However, through the works to organize grounds that had been accumulated through previous studies and evaluate and integrate the grounds, the general orientations of treatment effects of different treatment methods could be identified and presented.

Among the primary anticancer chemotherapies in diverse combinations

tried on patients with cancer of unknown primary sites, clear extensions of survival periods and improvement of survival rates were observed in the case of complex anticancer chemotherapy including taxane. Survival outcomes when taxane and platinum were used in combination were better than when taxane combination treatment that did not include platinum or platinum combination treatment that did not include taxane was used and much better than when other combination treatments that did not include taxane nor platinum and this can support the hypothesis that the optimal combination is the combination of taxane and platinum.

These results can be utilized as basic grounds for selecting primary complex anticancer chemotherapies for patients with cancer of unknown primary sites and also can be utilized as basic information necessary for creating ground data through additional clinical studies.