2019 Health Technology Reassessment Report

Safety and Effectiveness Reassessment of Transarterial radioembolization

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Summary (English)

▫ Assessment background

Transarterial radioembolization (TARE), which uses irradiation inside the body by injecting microspheres including radioisotopes into the hepatic artery, is a procedure used to treat tumor in patients with primary or metastatic liver cancer who cannot be treated by surgical resection or local treatment or failed chemotherapy. This

technique was recognized as a new health technology in 2010 and has been registered as a non-coverage item.

▫ Committee operation

A subcommittee consisting of five members held a total of four subcommittee sessions over a 4-month period between April and July 2019 to submit the results of assessment and review of this procedure based on literary evidence.

▫ Assessment objectives and methods

A systematic literature review was performed to assess the evidence for the safety and effectiveness of TARE. Detailed study methods were as follows and all assessment methods were established through review and approval by the "TARE Safety and Effectiveness Assessment Subcommittee" (*hereinafter* the Subcommittee) with consideration for the study objectives.

For systematic literature review, five Korean and three foreign databases were searched based on the key question above. Two reviewers independently screened and selected the articles according to the selection and exclusion criteria. Risk of bias assessment was performed independently by two reviewers using RoBANS until an agreement was reached. Data were extracted independently by two reviewers using pre-determined format. If there was a disagreement between the reviewers, such cases were discussed with a third party to reach an agreement. Meta-analysis was performed when quantitative analysis was possible and qualitative review was applied when otherwise.

Table 1-1 Details of PICO-TS

Item	Detail
Patients	Primary liver cancer Metastatic liver cancer

Item	Detail
Intervention	Transarterial radioembolization (TARE)
Comparators	Anticancer chemotherapy Transarterial chemoembolization (TACE) Hepatic artery embolization (HAE) Sorafenib
Outcomes	○ Safety Postoperative mortality within 30 days Adverse events and complications (postoperative morbidity) ○ Effectiveness Survival rate Local treatment effect: Objective response rate (ORR) Disease progression: Disease control rate (DCR) Quality of life (QoL) Time to progression to tumor
Follow-up period (Time)	No limit
Study type	Randomized clinical trial (RCT), non-RCT, and prospective comparative observational study
Years	2009 ~ present

▫ Assessment results

A total of 18 articles were used in the assessment, which included 16 articles selected from searching domestic/foreign databases according to predetermined protocol and two articles used to at the time of new health technology assessment.

Safety

Of six studies that compared TARE and TACE, two articles that reported on postoperative mortality within 30 days had no cases of mortality within 30 days. Postoperative morbidity was reported in five articles, but two RCTs and one prospective cohort study reported no difference in incidence of grade 3 or higher toxicity between the two groups. One non-RCT and prospective cohort study each reported that incidence of some adverse effects, such as nausea/vomiting, fatigue, and pain, was significantly lower in the TARE group.

Two RCTs that compared TARE and sorafenib did not report on postoperative mortality within 30 days and reported on only postoperative morbidity. Among a total of 408 patients in the TARE group,

grade 3 or higher radiation hepatitis and radiation pneumonia was found in 2 (1.5%) and 1 (< 1%) cases, respectively.

One RCT that compared TARE and hepatic artery embolization (HAE) reported on postoperative morbidity. One (20%) case of cholecystitis that required hospitalization occurred in the HAE group, and as a result, the TARE group had a significantly shorter hospital stay (p=0.024).

Among three RCTs that compared combination therapy with chemotherapy and TARE and chemotherapy alone, only one article reported on postoperative mortality within 30 days, but postoperative mortality within 30 days did not occur in both groups. Among three RCTs, one article reported that four (1%) cases of radiation hepatitis was found among 507 patients in the TARE group. In that article, eight and three cases of postoperative mortality were found in the TARE combination therapy and chemotherapy only groups, respectively.

One RCT that compared combination therapy with sorafenib and TARE and sorafenib alone therapy reported one incidence of grade 3 or higher toxicity as postoperative morbidity, but there were no items that showed significant differences between the two groups.

Effectiveness

Among the studies that compared with TACE among patients with primary liver cancer, one non-RCT reported on 1-, 2-, and 3-year survival rates; 59%, 40%, and 31% in the TARE group and 64%, 36%, and 11% in the TACE group, respectively. Among the five articles that reported on overall survival (OS) period, two RCTs and one non-RCT reported no difference in OS between the two groups, whereas significantly longer survival period was reported in the TACE group in one prospective cohort study and in the TARE group in another prospective cohort study. With respect to ORR, one RCT reported on response and progression rates based on best response, where ORR and DCR was 30.8% and 77% in the TARE group and 13.3% and 73.3% in the TACE group, respectively. In a meta-analysis of four non-RCTs, the results showed no differences in ORR (p=0.11) and DCR (p=1.00) between the two groups. In one RCT, there was a significant difference in time to progression to tumor with ≥ 26 months (median values was not observed during the follow-up period) in the TARE group and 6.8 months in the TACE group (p=0.0012), while one RCT and one non-RCT reported no significant difference between the two groups. In one RCT on QoL, there were significant differences in the initial physical function scores between the two groups (p=0.04), but there were no differences in the physical function and overall scores after 12 weeks.

There were two articles that reported on comparison between TARE and sorafenib among patients

with primary liver cancer and both articles were from RCTs. In both articles, survival rate was a hazard ratio (95% CI, p-value) of 1.12 (0.9-1.4, p=0.36) and 1.15 (0.94-1.41, p=0.18), showing no significant difference between TARE and sorafenib groups. When the OS and PFS periods presented in the two articles were quantitatively synthesized, the results showed no heterogeneity. OS was significantly shorter in the TARE group with 1.9 months (p=0.04), whereas there was no significant difference in PFS (p=0.98). ORR was higher in the TARE group with 16.5~19%, as compared to 1.7~12% in the sorafenib group (I^2=86%, OR 3.03, 95% CI 1.91-4.80, p<0.0001), whereas there was no differences in DCR between the two groups (41.8~68% vs. 42.7~78%; I^2=0%, OR 0.90, 95% CI 0.64-1.27, p=0.56). One article report time to progression to tumor with HR of 0.88 (95% CI 0.7-1.1, p=0.29), showing no statistically significant difference between the two groups. In one article that reported on QoL, the TARE group showed significantly better overall QoL score and the difference between the two groups increased over time, whereby QoL in the TARE group became better.

One prospective cohort study that compared TARE and TACE in patients with metastatic liver cancer (neuroendocrine tumor) reported on survival period, local treatment effect, and disease progression. The median OS period was 17.7 months in the TARE group and 25 months in the TACE group, while the median PFS period was 14 months in the TARE group and 18 months in the TACE group. ORR and DCR were presented at different time points (3, 6, 12, 18, and 24 months), with the TARE group showing CR of 6.7~13.3%, PR of 33.3~93.3%, ORR of 46.6~100%, and DCR of 53.3~100% and the TACE group showing CR of 0~10.7%, PR of 39.3~100%, ORR of 64.3~100%, and DCR of 67.9~100%.

One RCT that compared with HAE in patients with metastatic liver cancer (neuroendocrine tumor) reported on local treatment effect. There was a significant difference in ORR at 3 months with 0% in the TARE group and 100% in the HAE group (p=0.0022), whereas there was no significant difference in ORR at 6 months with 33.3% in the TARE group and 80% in the HAE group (p=0.24).

Among three RCTs that compared combination therapy with TARE and chemotherapy and chemotherapy alone in patients with metastatic liver cancer (colorectal cancer), two studies reported no difference in survival rate between the two groups (n=1,103, HR 1.04, 95% CI 0.90-1.19, p=0.61; n=44, HR 0.92, 95% CI 0.47-1.78, p=0.8), whereas one study reported that survival rate was significantly higher in the combination therapy (including TARE) group (n=21, HR 0.33, 95% CI 0.12-0.91, p=0.025). Three studies reported median OS period of 10~29.4 months in the combination therapy group and 7.3~23.3 months in the chemotherapy alone group. Meanwhile, one study reported median PFS period of 11 months in the combination therapy group and 10.3 months in the

chemotherapy alone group. All three studies reported on local treatment effect and disease progression and meta-analysis results showed significantly higher ORR in the combination therapy group (I^2=64%, OR 1.65, 95% CI 1.28-2.12, p<0.0001) and no significant difference in DCR between the two groups (I^2=84%, OR 1.26, 95% CI 0.89-1.78, p=0.19). Two articles reported on time to progression to tumor, indicating that time to progression to tumor was significantly longer in the combination therapy group with one article reporting 5.5 months in the combination therapy group and 2.1 months in the standalone therapy group (HR 0.38, 95% CI 0.20-0.72, p=0.003) and the other article reporting 18.6 months in the combination therapy group and 3.6 months in the standalone therapy group (p<0.0005). One article reported on QoL, in which, measurement of QoL at baseline, 2-3, 6, 12, and 24 months showed significantly lower QoL at 2-3 months in the TARE group (p=0.038) and no significant differences in QoL between the two groups at all other time points.

▫ Conclusions

Based on currently available literature, the TARE subcommittee is presenting the following results in regard to safety and effectiveness of TARE in patients with primary or metastatic liver cancer.

In the comparison between TARE and TACE in patients with primary liver cancer, the results were similar for safety indicators postoperative mortality within 30 days and postoperative morbidity. The overall results were also similar for effectiveness indicators survival rate, survival period, ORR, DCR, time to progression to tumor, and QoL, but some articles reported that ORR and DCR were higher and time to progression to tumor was longer in the TARE group. Although the results of comparison between TARE and TACE in patients with primary liver cancer showed differences in some effectiveness indicators, the subcommittee determined that there were no major differences in the overall safety and effectiveness.

In the comparison between TARE and sorafenib in patients with primary liver cancer, the results were similar for safety indicator postoperative morbidity and effectiveness indicators survival rate, DCR, time to progression to tumor, and QoL. Among patients with primary liver cancer, ORR and QoL were higher in the TARE group, while OS period was slightly longer in the sorafenib group. The subcommittee determined that additional evidence with consideration of appropriate selection of patient groups and heterogeneity among articles is needed and that survival period and QoL need to be considered when comparing and selecting TARE and sorafenib in patients with primary liver cancer.

In the comparison between combination therapy with TARE and sorafenib and sorafenib alone, the results were similar for postoperative morbidity. However, the subcommittee determined that it would

be difficult to assess safety due to insufficient number articles and the low level of evidence in the articles that compared combination therapy with TARE and sorafenib to sorafenib alone.

In the comparison between TARE and TACE in patients with metastatic liver cancer from neuroendocrine tumor, the results were similar for safety indicators postoperative mortality within 30 days and postoperative morbidity and effectiveness indicators survival rate, response rate, and disease progression rate. However, because these results were reported in just one article with low level of evidence, the subcommittee determined that assessment would be difficult due to insufficient evidence from comparison between TARE and TACE in patients with neuroendocrine tumor metastatic liver cancer.

In the comparison between combination therapy with TARE and sorafenib and sorafenib alone in patients with neuroendocrine tumor metastatic liver cancer, the results were similar for postoperative morbidity and effectiveness indicator ORR. However, because the results were from a single article with small sample size and did not sufficiently report effectiveness results, the subcommittee determined that safety and effectiveness assessment would be difficult based on comparison between combination therapy with TARE and sorafenib and sorafenib alone in patients with neuroendocrine tumor metastatic liver cancer.

In the comparison between combination therapy with TARE and chemotherapy and chemotherapy alone in patients with metastatic liver cancer from colorectal cancer, the results were similar for postoperative mortality within 30 days and postoperative morbidity. Among effectiveness indicators, ORR was superior, but there were no significant differences in survival period, DCR, time to progression to tumor, and QoL. Accordingly, the subcommittee determined that there is insufficient clinical evidence to support that combination therapy with TARE and chemotherapy has superior effectiveness than chemotherapy alone in patients with colorectal cancer metastatic liver cancer.

Based on the conclusions above and current assessment results, the TARE subcommittee proposed the following. In the comparisons of TARE and other treatment modalities in patients with primary or metastatic liver cancer, the overall safety level was acceptable, but evidence for effectiveness is currently insufficient.

The Health Technology Reassessment Committee reviewed and determined that the findings of the subcommittee on TARE are valid (September 20, 2019).