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Single-bolus regional chemotherapy with doxorubicin versus chemoembolization in a rabbit VX2 tumor model

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PURPOSE
This study evaluates the anti-tumor effect of regional chemotherapy compared with chemoembolization in an animal model.

MATERIALS AND METHODS
Twenty-one rabbits bearing VX2 liver tumors were divided into the following four groups: (a) the transarterial (TA) group (n=6) received a transarterial injection of doxorubicin through the hepatic artery (1 mg/kg); (b) the transarterial and transportal (TAP) group (n=6) received injections of doxorubicin through both the hepatic artery (1 mg/kg) and the portal vein (1 mg/kg); (c) the transarterial chemoembolization (TACE) group (n=6) received a transarterial injection of doxorubicin (1 mg/kg) followed by gelatin sponge embolization; and (d) the control group (n=3) received no treatment. With the use of computed tomography, tumor growth rates were calculated and microscopic examinations were performed to evaluate the extent of tumor necrosis.

RESULTS
Seven days after each treatment, the mean tumor growth rates were 216.7%±189.0% in the TA group, 77.1%±73.9% in the TAP group, and 489.5%±352.1% in the control group; there were no significant differences in tumor growth rates ($P = 0.057$). The tumor growth rate of the TACE group could not be evaluated due to extensive liver necrosis. The mean tumor necrosis rates were 41.9%±11.5% in the TA group, 51.4%±11.1% in the TAP group, 94.7%±3.5% in the TACE group, and 29.3%±6.7% in the control group; the TACE group showed significantly higher tumor necrosis than any other groups.

CONCLUSION
Single session regional chemotherapy has limited anti-tumor effects when compared with TACE in the rabbit VX2 tumor model.

Key words: • chemoembolization, therapeutic • infusion, intra-arterial • portal vein • liver neoplasms, experimental

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Transarterial chemoembolization (TACE) is the most commonly used palliative treatment for patients with hepatocellular carcinoma (HCC) who are not eligible for curative treatments. TACE combines targeted chemotherapy with arterial embolization. The therapeutic benefits of TACE have been confirmed, and TACE has become the standard treatment for selected patients (1–3).

Although its therapeutic benefits have been confirmed, TACE is associated with a wide variety of complications. Hepatic failure is one of its most serious complications, and occurs when arterial embolization associated with TACE causes ischemic damage to liver tissue. Approximately 3% of patients were reported to have developed irreversible hepatic decompensation following TACE (4). One might consider performing transarterial chemotherapy alone to avoid the hepatotoxicity and hepatic failure that can result from embolization; however, the therapeutic efficacy of transarterial chemotherapy alone is inferior to that of TACE (5, 6).

Although transportal administration of therapeutic agents has been experimentally and clinically investigated as an adjuvant treatment method for primary or secondary liver cancers (7–9), the transportal approach has been underutilized in practice because HCC derives most of its blood supply from the hepatic artery. However, portal vein tumor thrombi are usually nourished by the portal vein. The periphery of HCC nodules or an advanced HCC with extracapsular invasion has a dual blood supply that is derived from both the hepatic artery and the portal vein (10–12). The portal venous supply to these tumors suggests that a transportal approach may aid in the treatment of liver tumors, especially advanced liver tumors (7, 8, 13).

Our hypothesis was that concurrent administration of transportal chemotherapy and transarterial chemotherapy increases the therapeutic efficacy of transarterial chemotherapy while mitigating the hepatic toxicity and hepatic failure of embolization. The aims of this study were to test whether the combination of transarterial and transportal chemotherapy results in synergistic anti-tumor effects and to compare these effects with those of TACE in a rabbit VX2 tumor model.

Materials and methods

Animal liver tumor model and experimental groups

Approval for this study was obtained from the Research Animal Use Committee of our institution. Twenty-one New Zealand white rabbits (Biogenomics, Seoul, Republic of Korea) weighing 2.0–2.5 kg were used. The VX2 tumor strain had been maintained by means of successive percutaneous transplantation into the hind leg muscle of a carrier rabbit. Prior to all procedures, anesthesia was induced by intramuscular injection of a mixture of ketamine hydrochloride (35 mg/kg of body weight; Ketalar, Yuhan Yanghang, Seoul, Republic of Korea) and xylazine hydrochloride

(5 mg/kg; Rompun, Bayer Korea, Seoul, Republic of Korea). Anesthesia was maintained with repeated intravenous injections of the same mixture when necessary. Because transcatheter therapy, including TACE, is usually indicated for the treatment of intermediate or advanced tumors rather than for curable small HCCs (1–3), we selected the transportal route for tumor inoculation because transportal tumor inoculation usually induces diffuse tumor involvement (14). A VX2 tumor, having been grown for two weeks in the hind leg muscles of carrier rabbits, was excised, and chunks of the tumor were minced in Hanks' solution (15). Through a midline abdominal incision, a small branch of the superior mesenteric vein was cannulated with a 4-Fr sheath (Terumo, Tokyo, Japan), and a 3-Fr microcatheter (Microferret, Cook, Bloomington, Indiana, USA) was inserted into the lateral segmental branch of the left portal vein, which usually had a luminal diameter sufficient to localize the microcatheter (16). Next, approximately 0.1 mL of the minced VX2 tumor was injected through the microcatheter. Prior to tumor injection, contrast medium was slowly and manually injected into the selected branch of the portal vein to approximate the speed of tumor injection. Free regurgitation of portal venous blood was always confirmed to avoid efflux of the tumor. All procedures were performed under fluoroscopy guidance, and the tumor injection did not result in embolization of the selected segmental portal vein branch. To maintain the VX2 tumor strain, another 0.1 mL of the minced VX2 tumor was percutaneously transplanted into the hind leg muscle of a carrier rabbit using an 18G needle.

One day before each therapeutic procedure (thirteen days after tumor inoculation), CT examinations were performed according to a protocol using a helical CT scanner (Lightspeed 16, GE Medical Systems, Milwaukee, Wisconsin, USA) that was previously described by Kim et al. (17). Briefly, after injection of 15 mL of contrast agent (Iopromide, Ultravist, Schering, Berlin, Germany) at a rate of 0.5 mL/s through the auricular vein, post-contrast CT scans were obtained 20–30, 50–60, and 90 s after initiation of contrast agent injection. The parameters of the CT scans were 2.5-mm slice thicknesses and 2.5-mm intervals. Anesthesia was maintained as described above during the CT examinations.

On CT images, tumor sizes were measured using an electronic caliper. The tumor volume (V) was calculated according to the equation $V=L\times S^2/2$, where L is the longest diameter and S the shortest diameter of the tumor (18). When multiple tumors were formed, the volumes of the largest tumors (up to three) with clear margins were measured and summed.

The 21 rabbits were divided into four groups: (a) the transarterial (TA) group (n=6) received a transarterial injection of doxorubicin (1 mg/kg of body weight; Ildong, Seoul, Republic of Korea); (b) the transarterial and transportal (TAP) group (n=6) received an injection of doxorubicin through both the hepatic artery (1 mg/kg) and the portal vein (1 mg/kg), thus receiving a total of 2 mg/kg of doxorubicin; (c) the TACE group (n=6) received a transarterial injection of doxorubicin (1 mg/kg) followed by gelatin sponge (Cutanplast, Mascia Brunelli, Milan, Italy) embolization; and (d) the control group (n=3) received no treatment.

Therapeutic procedures

Two weeks after tumor inoculation, when the tumor diameter was expected to be >5 mm (13), the animals underwent the appropriate therapeutic procedures. Surgical cut-down of the common femoral artery was performed, and a 4-Fr sheath was placed into the femoral artery. After catheterization of the celiac axis with a 3-Fr microcatheter, the microcatheter was negotiated into a position in the left hepatic artery, which usually provided most of the blood flow to the tumor. For the TA group, 10 mg of doxorubicin were dissolved in 10 mL of iopromide (1 mg/mL). Transarterial doxorubicin infusion (1 mg/kg) was performed using the microcatheter under fluoroscopy guidance. For the TACE group, doxorubicin infusion was followed by gelatin sponge embolization; the gelatin sponge was manually cut into pieces of approximately 1 mm^3 and mixed with a small amount of iopromide. Embolization was performed until the blood flow of the left hepatic artery ceased. The catheter and sheath were then removed, and the femoral artery was ligated.

For the TAP group, both transarterial and transportal injections were performed during the same session. The process of transarterial doxorubicin injection (1 mg/kg) was the same as that used for the TA group and usually preceded transportal injection. Transportal injection of doxorubicin was conducted similarly to tumor inoculation; after a midline abdominal incision was made, a small branch of the mesenteric vein was cannulated using a 4-Fr sheath. A 3-Fr microcatheter was negotiated into the left portal vein, followed by injection of doxorubicin (1 mg/kg) through the catheter. Doxorubicin solution was prepared in the same manner as in the TA group. All injections were performed slowly, over the course of a few minutes, so as not to cause overflow from the targeted vessels. After removal of the catheter and sheath, bleeding was controlled by either compression or ligation.

Evaluation of anti-tumor effects

Follow-up CT examinations were performed 7 days after each treatment to measure post-treatment tumor volumes when the tumor necrosis rates were expected to be over 90% after TACE (19). Then, the animals were sacrificed, and their livers were explanted. Both macroscopic and microscopic methods were used to evaluate the anti-tumor effects. Macroscopically, tumor growth rates (%) were calculated by comparing the tumor volumes obtained before (V_b) and 7 days after (V_7) treatment using the formula (V_7/V_b-1)×100. For microscopic evaluations, explanted livers were fixed in 10% formalin solution, and the liver tissue containing the tumor was sliced at 2–5 mm intervals (depending on tumor size) and stained with hematoxylin-eosin. Tumor viability and the extent of tumor necrosis were evaluated by visual inspection of representative slides (usually 6–7 slides per tumor) by a pathologist. To quantify the antitumor effects, the proportion of the area of tumor necrosis compared to that of the entire tumor was estimated. The overall percentage of tumor necrosis was calculated on the basis of the average percentage for each slice.

Measurement of plasma biochemical parameters

To determine the extent of hepatic and hematologic toxicities caused by the treatments, peripheral blood was drawn via the auricular vein from all rabbits (except for rabbits in the control

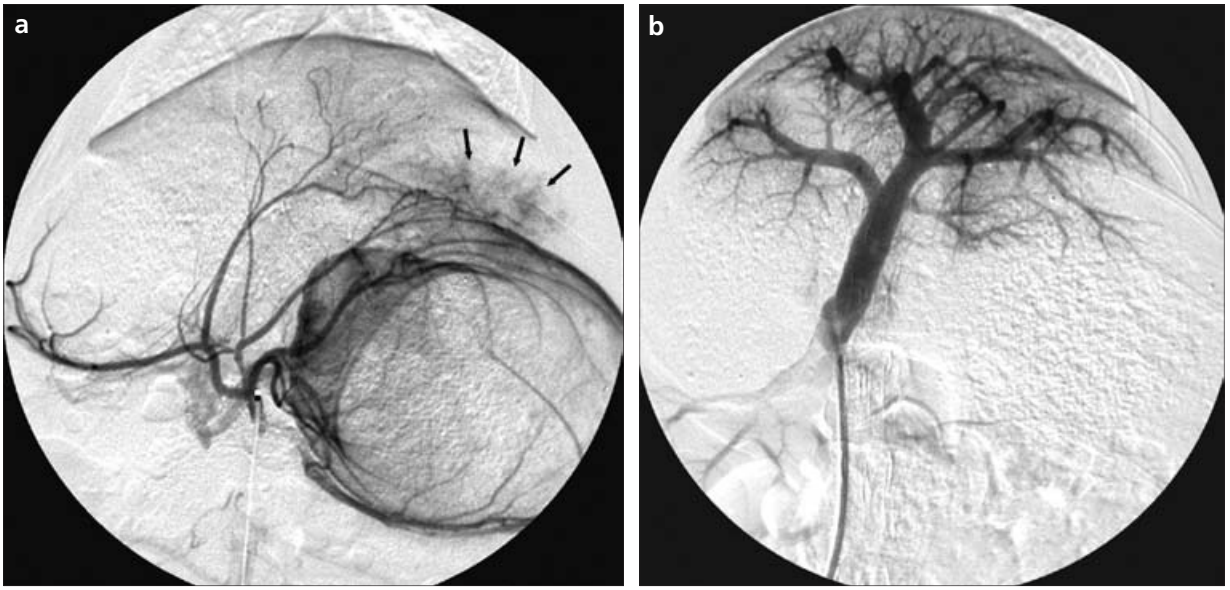

Figure 1. a, b. A hepatic arteriogram and portal venogram of a rabbit, obtained two weeks after transportal tumor inoculation. The hepatic arteriogram **(a)** shows the presence of ill-defined hypervascular tumor staining in the left lobe *(arrows).* The portal venogram **(b)** appears normal, with no tumor staining or vascular abnormality.

group) before and 1, 2, 3, and 7 days after each treatment. The following biochemical parameters were measured using a biochemical autoanalyzer (Hitachi 7150, Tokyo, Japan): plasma aspartate aminotransferase (AST) levels, alanine aminotransferase (ALT) levels, total bilirubin levels, and blood cell counts.

Statistical analysis

Anti-tumor effects and plasma biochemical parameters were analyzed using the Kruskal-Wallis test and Mann-Whitney U-test (Statistical Package for Social Sciences version 11.5, SPSS Inc., Chicago, Illinois, USA). A P value <0.05 was considered to indicate a significant difference (two-tailed test).

Results

Animal liver tumor model

After transportal tumor inoculation, a single nodular tumor in the left lobe of the liver was observed in 10 animals, and multinodular tumors in the left lobe of the liver were observed in 11 animals, as determined by CT scans performed 13 days after tumor inoculation. While hypervascular tumor staining was noted on hepatic arteriograms, portal venograms appeared normal, even though tumor inoculation had been performed through the portal vein (Fig. 1). The longest diameter of each tumor ranged from 5–28 mm (median, 15.0 mm). Tumor volumes ranged from 647.8 to 3526.7 mm^3 (mean, 2451.2±1198.7 mm^3) in the TA group, 822.2–3051.2 mm^3 (mean, 1874.5±865.4 mm^3) in the TAP group, 1453.1–3905.6 mm^3 (mean, 2372.6±884.4 mm^3) in the TACE group, and 845.6–3318.9 mm^3 (mean, 2148.8±1242.0 mm^3) in the control group. Tumor volumes were not significantly different among the four groups (P = 0.853).

Therapeutic procedures

All procedures were performed successfully in all animals. One animal in the TACE group died two days after TACE. Although intra-abdominal adhesions due to previous tumor implantation procedures were noted in rabbits of the TAP group, the adhesions did not interfere with the cannulation of any suitable mesenteric vein branch or with the performance of transportal drug injection.

Anti-tumor effects

The mean tumor growth rates 7 days after the therapeutic procedures were 216.7%±189.0% (range, 44.0%–502.6%) in the TA group, 77.1%±73.9% (range, 24.0%–223.0%) in the TAP group, and 489.5%±352.1% (range, 84.0%–717.9%) in the control group. In the TA, TAP, and control groups, the most common finding on follow-up CT examinations was conglomerated tumor growth, which was hypodense compared to the surrounding liver (Fig. 2). The tumor growth rate of the TACE group could not be evaluated because follow-up CT images showed extensive liver necrosis, making the boundary between the liver and the tumor indiscernible in four out of five surviving animals in that group (Fig. 2). The tumor growth rate of the one animal without extensive liver necrosis in the TACE group was estimated to be -14.5%. Tumor growth rates were not significantly different (P = 0.057) among the TA, TAP, and control groups.

Upon microscopic examination, tumors treated with TACE showed massive coagulation necrosis involving both the peripheral and central regions of the tumors, usually accompanied by necrosis of the adjacent liver tissue. In contrast, tumors of the other groups invariably consisted of numerous viable tumor cells, with only partial necrosis that was characterized by a comedo-like pattern at the center of the tumor cell nest (Fig. 3). The mean tumor necrosis rates were 41.9%±11.5% (range, 32.3%–57.5%) in the TA group, 51.4%±11.1% (range, 36.3%–63.0%) in the TAP group, 94.7%±3.5% (range, 92.0%–100%) in the TACE group, and 29.3%±6.7% (range, 21.5%–35.0%) in the control group (Fig. 4). Complete tumor necrosis was only noted in one animal in the TACE group. Tumor necrosis rates differed significantly among the four groups (P = 0.003), and

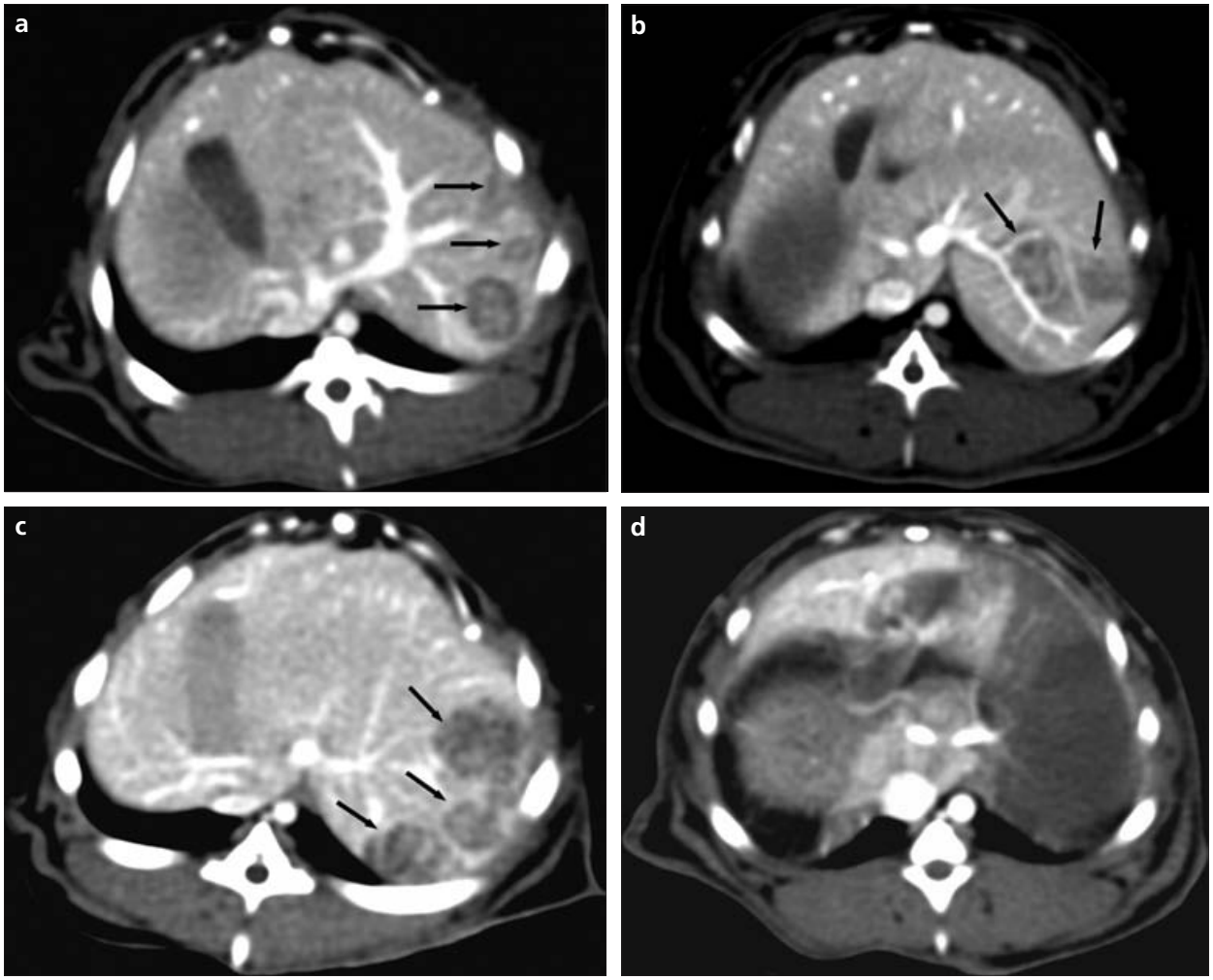

Figure 2. a–d. CT scans of VX2 liver tumors in the TA and TACE groups. Contrast-enhanced CT images obtained before each treatment **(a,** TA group; **b,** TACE group**)** reveal low-attenuated tumors in the left lobe of the liver *(arrows).* Seven days after treatment, tumors of the TA group **(c)** show marked conglomerated growth, and contrast enhancement is seen in most portions of the tumor area. CT after TACE **(d)** shows extensive low attenuation in the left lobe, indicating necrosis of the tumor and surrounding liver. The border between the liver and the tumor is indistinguishable.

the TACE group showed significantly higher tumor necrosis than any other group ($P = 0.006$ vs. TA; $P = 0.006$ vs. TAP; and $P = 0.025$ vs. control). The TAP group showed significantly higher necrosis than the control group ($P = 0.021$); however, no other significant difference was noted ($P = 0.240$ for TA vs. TAP; $P = 0.121$ for TA vs. control).

Toxicity

Fig. 5 shows the plasma levels of AST and ALT before and after each treatment. In general, the levels peaked the day after treatments and decreased gradually thereafter. There was a delayed rise in ALT levels in the TACE group, but the significance was unknown, as a follow-up analysis was not performed. ALT levels seemed to be higher in the TACE group; however, the finding was not significant ($P = 0.275$ for AST; $P = 0.471$ for ALT). Total plasma bilirubin levels and blood cell counts did not change appreciably in any of the groups.

Discussion

For regional chemotherapy of liver tumors, transarterial and, less commonly, transportal access have been utilized as vascular routes of chemotherapy administration (7–9, 13). However, little has been reported on the usefulness of the combined use of these two routes compared to the use of TACE alone. Transarterial treatments cannot be used to eradicate tumor cells in portal tracts or the peripheral and extracapsular portions of advanced HCCs that derive their blood supplies from portal veins (7, 10–12). We hypothesized that the transportal delivery of chemotherapy could address these limitations of transarterial therapy. Therefore, the combined transarterial and transportal approach may strengthen the therapeutic efficacy of regional chemotherapy, which has traditionally been considered inferior to TACE (5). In the present study, a tendency toward better anti-tumor effects was observed for the TAP group compared to the TA group; however, this tendency failed to reach significance. In experimental models, the blood supply to liver tumors varied with tumor size: tumors greater than 1 cm in diameter derive most of their blood supply from the hepatic artery; tumors between 0.5 and 2 mm in diameter are mainly vascularized by the portal system; and tumors of approximately 5 mm in diameter obtain their blood supply from both hepatic and portal circulation (20, 21). In our study, the

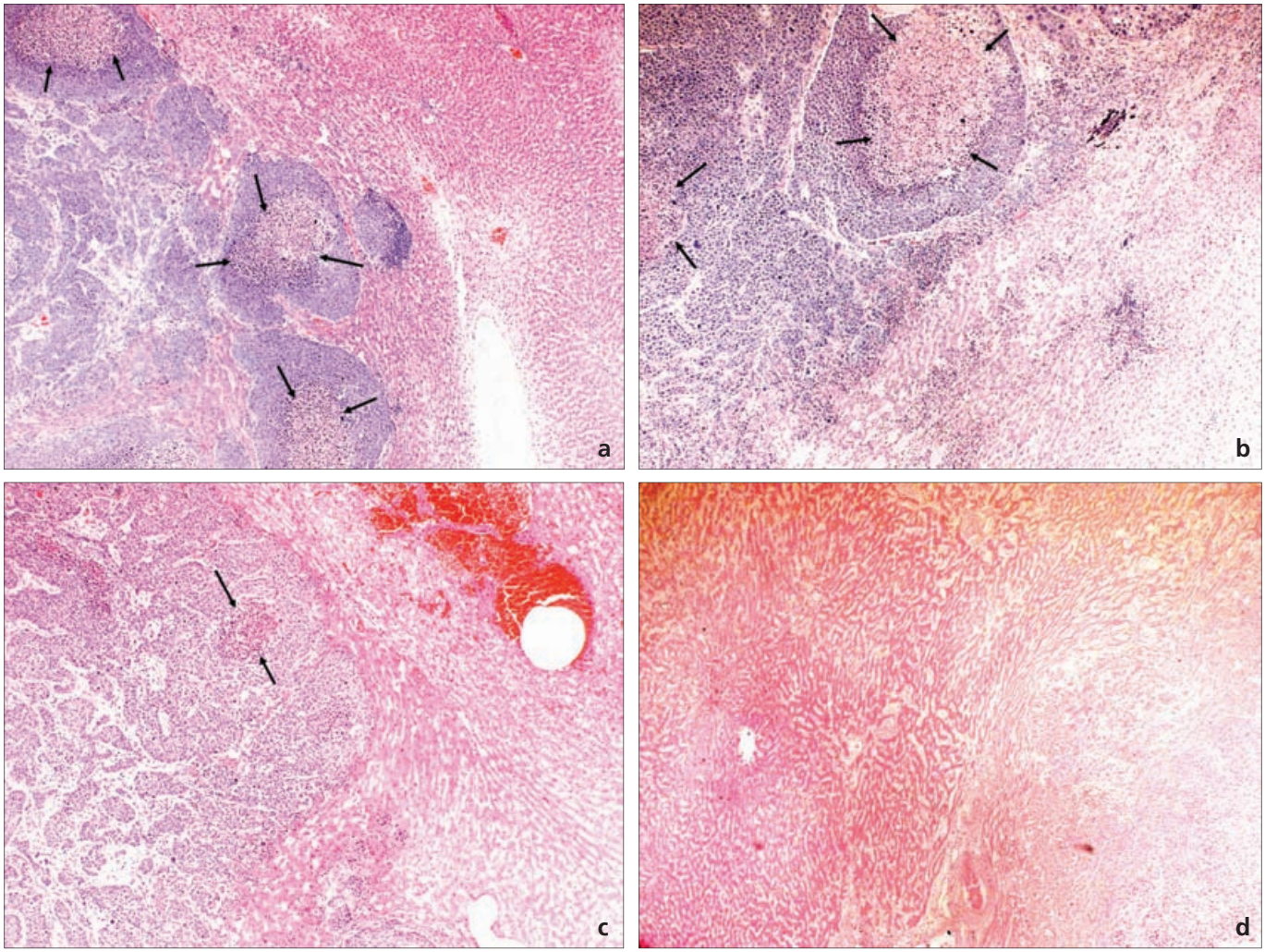

Figure 3. a–d. Microscopic findings of liver tumor in rabbits from each group (x40, hematoxylin-eosin). Tumor tissues of the TA **(a)**, TAP **(b)**, and control **(c)** groups show only partial central necrosis *(arrows)*. However, in the TACE group, tumor tissue underwent massive necrosis, with no viable tumor cells. Necrosis of the adjacent liver tissue is also noted **(d)**.

hepatic artery was likely the dominant tumor feeder, as the median tumor size was 15.0 mm, and hepatic arteriograms showed tumor staining in all animals. This vascular supply pattern may detract from the therapeutic effects of transportal chemotherapy and may be a reason for the lack of statistically significant advantage of the antitumor effects of the combined regional chemotherapy compared to transarterial chemotherapy alone. In an experimental model of liver metastasis, Ramirez et al. (13) demonstrated that transportal chemotherapy suppressed not only intrahepatic tumor growth but also extrahepatic tumor dissemination. However, it is noteworthy that transportal chemotherapy was shown to be beneficial only in early-stage tumors when tumor nodules were only detectable microscopically (13).

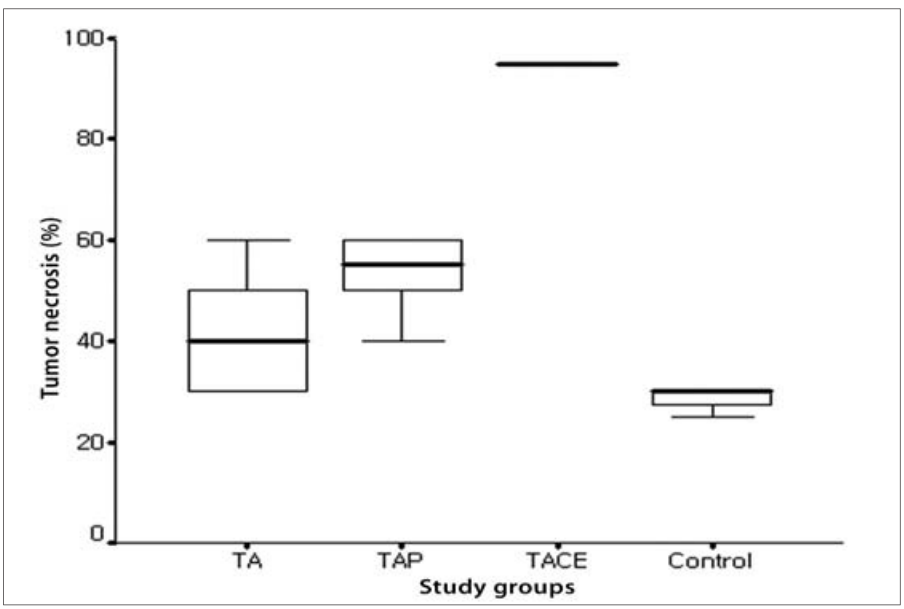

Figure 4. The mean tumor necrosis rates which were determined microscopically. The TACE group was the only group that revealed significantly higher tumor necrosis when compared with other groups ($P = 0.006$ vs. TA; $P = 0.006$ vs. TAP; and $P = 0.025$ vs. control).

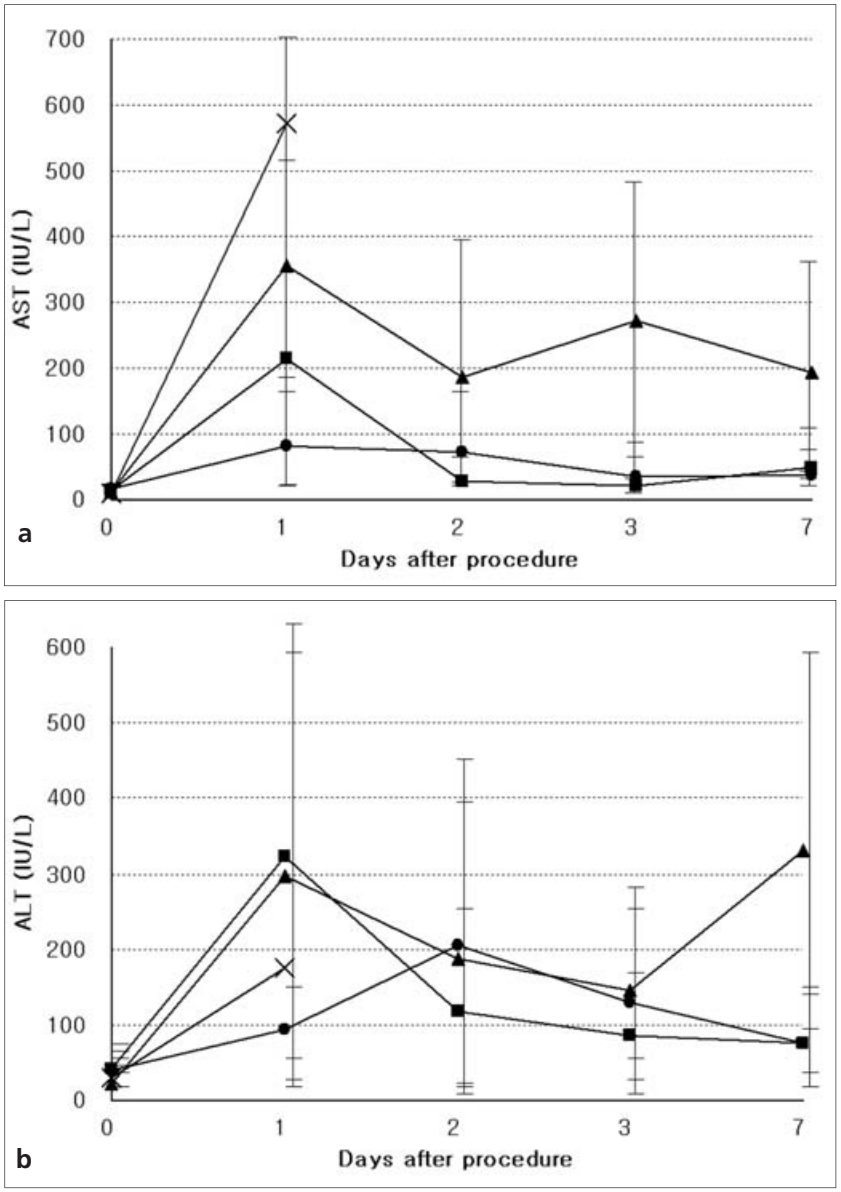

Figure 5. a, b. Changes in plasma aspartate aminotransferase **(a)** and alanine aminotransferase **(b)** levels. Graphs show that the levels peaked the day after treatment and tended to decrease thereafter. The levels of the TACE group seem to be high compared to all other groups, although this trend was without statistical significance. (■, TA group; ●, TAP group; ▲, TACE group; ×, one animal that died two days after TACE.)

We found that the tumor necrosis rate of the TACE group was significantly higher than the rates of the other groups. In a comparative study by Pauser et al. (19), combinations of transarterial chemotherapy with embolization (degradable starch microspheres and gelatin sponges) were compared with either transarterial chemotherapy alone or embolization alone in a liver VX2 tumor model. The combination of chemotherapy and embolization was significantly more efficient than the other treatments, inducing almost complete tumor necrosis. It should be noted that significant tumor growth was observed for all therapy groups except the group treated with transarterial chemotherapy and gelatin sponge embolization, which induced a reduction in tumor volume (19). Another comparative study by Yamashita et al. (22) showed that the anti-tumor effects of gelatin sponge embolization with or without regional chemotherapy were the most effective compared to the effects of the combination of iodized oil and chemotherapy, regional chemotherapy alone or iodized oil alone. The authors noted that the role of chemotherapy was of little importance in animals treated with gelatin sponge embolization. These results together with our results suggest that embolization rather than chemotherapy is the predominant therapeutic component of TACE. Alternatively, chemotherapy might need to be combined with embolization to exert substantial chemotherapeutic effects in TACE.

The growth pattern of VX2 tumors in the liver differs according to the particular method of tumor implantation. After direct tumor implantation into the liver parenchyma, VX2 tumor growth is localized. With tumor injection into the hepatic artery or portal vein, tumor involvement is diffuse, and the tumor grows aggressively (14). In our study, the tumor was innoculated through the portal vein because we wanted to establish a locally advanced tumor model. However, we observed that a single nodular tumor was formed in almost 50% of the animals. This localized tumor growth may have resulted from our tumor implantation technique because tumor inoculation was performed at a segmental branch of the portal vein rather than at the main portal vein or superior mesenteric vein.

With regard to hepatic toxicity, we found that plasma levels of AST and ALT were not significantly different among the three groups within one week after each treatment. However, the increases in the levels of AST and ALT were more prominent after TACE than after other treatments. Although this difference was not significant, the trend implies that TACE may cause substantial hepatic toxicity. One animal died two days after TACE. Although the cause of death was uncertain, it may have been due to hepatotoxicity because elevation of liver enzyme levels was the only abnormal finding in this animal. Necrosis of adjacent liver tissue was noted in the TACE group only; this finding correlated well with results of previous clinical and experimental studies in which liver necrosis and elevation of liver enzyme levels were more commonly observed following gelatin sponge embolization, regardless of whether regional chemotherapy was administered, compared to other transarterial treatments with no gelatin sponge embolization (22, 23).

This study had major limitations. First, we used a fixed dose regimen of a single drug. Doxorubicin was chosen

because it is one of the most widely used chemotherapeutic agents in clinical and experimental studies of liver tumors. A previous study reported that transarterial injection of 0.5 mg/kg doxorubicin resulted in significant growth suppression of VX2 liver tumors when compared with transarterial saline injection (24). Although the dose of doxorubicin used in this study (1 mg/kg) was determined considering that the tumor burden was more than two times greater than that of the previous study (24), the dose used may have been insufficient to induce maximal anti-tumor effects of regional chemotherapy. Further studies are needed to verify the anti-tumor effects of regional chemotherapy; such studies should adopt high-dose or multi-drug regimens or iterative treatments. Second, a small number of animals were included in each group, limiting the validity of the conclusions. Third, long-term follow-up results, including survival data, were not obtained; therefore, it is not clear whether the anti-tumor effects of TACE would lead to any survival benefit. Fourth, we did not use iodized oil, which is an effective drug carrier. A recent experimental study investigating the pharmacologic features of TACE for liver VX2 tumors showed that TACE using a cisplatin/iodized oil suspension and gelatin sponges had a number of pharmacologic advantages compared to transarterial chemotherapy with or without gelatin sponge embolization, implying the significance of iodized oil use in TACE (6). Because the aim of our study was to compare the anti-tumor effects of regional chemotherapy and TACE in terms of tumor necrosis and macroscopic tumor growth, we wanted to ensure that the conditions of each experimental group were as comparable as possible; therefore, we did not use iodized oil. However, the pharmacologic benefits of the use of a drug carrier in the context of TACE deserve further study to clarify whether the observed pharmacologic benefits will invariably lead to survival benefits. Lastly, tumor injection and growth in the portal vein may alter the microvascular architecture of the rabbit liver (25) and may affect the anti-tumor effects of the regimens tested.

In conclusion, single-session regional chemotherapy has limited anti-tumor effects when compared with TACE in a rabbit VX2 tumor model. Despite the theoretical advantages of the transportal approach, the combination of transarterial and transportal chemotherapy was found to have no synergistic anti-tumor effects in this experimental study. Though TACE seems to have better anti-tumor effects than regional chemotherapy, further investigations regarding how to minimize the hepatotoxicity of TACE are warranted.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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