LOCOREGIONAL/LIVER DIRECTED THERAPIES

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Given the dual blood supply to the liver, with the hepatic artery providing the majority of blood flow to tumors, and the portal vein providing trophic blood supply to the liver parenchyma[1], combined with the lack of other effective non-surgical treatments, it is not surprising that over the last 4 decades trans-arterial methods of treating unresectable hepatocellular carcinoma (HCC) have become a mainstay of therapy. One of the early reports of transcatheter management of HCC by Charnsangavej et al[2] in 1983 described results following 2 methods of treatment, the continuous hepatic arterial infusion (HAI) of floxuridine, doxorubicin and mitomycin C in 14 patients requiring a 5 day hospital stay with 2 courses of treatment given at 4-6 week intervals. The other group of 9 patients (2 of whom crossed over from the HAI group) was treated with hepatic artery embolization (HAE) using Ivalon (Unipoint Industries, High Point, NC). Response rates in the 2 groups were similar, 71% in HAI group vs. 67% in HAE group, with median survival of 12.3 months and 17.4 months, respectively. Later that year Yamada et al[3] described the use of gelatin sponge cut into 1-2mm pieces and "permeated" with mitomycin C or doxorubicin to treat 120 patients with HCC, infusing this chemotherapy soaked gelatin sponge into the artery feeding the tumor. The 1, 2 & 3-year cumulative survival rates were 44%, 29% and 15% respectively. In this paper the authors noted that given the knowledge that HCC derives blood supply from "only the hepatic artery"[1] embolization can be expected to result in selective necrosis of the tumor tissue and that, whereas the effect of the single dose of mitomycin or doxorubicin may have been enhanced, it is possible that ischemia might be the primary mechanism of tumoricidal effect[3]. In a 1987 study by Takayasu et al[4] patients with HCC were divided into 3 groups for intra-arterial treatment. Group A received intra-arterial Lipiodol (Guerbet USA, Bloomington, IN) alone, Group B an emulsion of Lipiodol with doxorubicin, and group C the same emulsion followed by embolization with gelatin sponge. Group C showed the best therapeutic effect, there was no significant difference in response between groups A & B, with practically no therapeutic effect from Lipiodol alone. Although these results can be interpreted a number of ways, the authors pointed out that the results achieved using the anticancer emulsion plus gelatin sponge were superior to those previously described for embolization with gelatin sponge and anticancer agents, and posited that the combination of Lipiodol blocking small vessels and gelatin sponge occluding more proximal feeding arteries resulted in an anoxic state "independent of drug sensitivity of the tumor". They also noted an association between uptake of Lipiodol by the tumor and therapeutic effect. In 1989 Nakamura described a similar effect on survival, comparing 100 patients treated with doxorubicin, iodized oil and gelatin sponge to 104 historical controls embolized with gelatin sponge and either doxorubicin (96) or mitomycin (8) achieving 1, 2 and 3 year survivals of 53, 33 and 18% in the iodized oil group and 45, 16

and 4% in those treated with only gelatin sponge plus chemotherapy. It seemed clear that transcatheter treatment of HCC brought about a radiologic response; the question of what the primary driver of that therapeutic effect was remained, as well as whether an imaging response to treatment would translate into improved survival.

Pharmacokinetic data supporting the use of intra-arterial chemotherapy, or chemotherapy plus lipiodol administered as an emulsion with an embolic agent, as commonly used today, is less than convincing. Studies clearly demonstrating high & prolonged concentration of chemotherapeutic agents within tumor were performed using mitomycin C, doxorubicin, and aclarubicin dissolved in hydrocarbon solvents and then in lipiodol[5], or using a lipophilic agent[6], methods which are not used clinically. In the animal study by Konno[5], when the chemotherapeutic agent was dissolved in water and then mixed with lipiodol and administered as an emulsion, concentration of drug in the tumor was high immediately, but low at 6 hours, 1 day and 7 days. In a study of 18 patients by Raoul et al[7] doxorubicin was given to patients intra-arterially using 3 different methods; alone as an infusion, emulsified with lipiodol, or with lipiodol and gelatin sponge. There was no significant difference in total amount of doxorubicin released into the circulating blood, but patients in whom gelatin sponge was used had less released within the first hour of treatment. Another study evaluated intraarterial doxorubicin vs doxorubicin with lipiodol[8], and found no difference in the area under the concentration-time curve, or terminal half life, and no difference in pharmacokinetic profile or systemic toxicity using the same dose schedule compared to administering the doxorubicin intravenously. Even if the pharmacokinetic profile was more encouraging, none of these anticancer agents had ever been demonstrated to have a significant effect on the survival of patients with HCC when administered intravenously making it difficult to know which agent, or which combination of agents, to use clinically. There are many embolic agents available for embolization. This has led to myriad methods of transcatheter intra-arterial therapy for HCC, limiting the ability to compare results between different groups. Meta-analysis by Simonetti et al in 1997[9] failed to support the effectiveness of non-surgical treatments for HCC but some evidence of "moderate benefit" emerged from trial using tamoxifen and transcatheter arterial embolization (without iodized oil). Combining the heterogeneous population of patients with HCC who present with varied etiology and stage of underlying liver disease, size and number of tumors, and vascular invasion status, with the diverse methods used to treat them, made it even more difficult to compare results of treatment between diverse investigators and there were no strong randomized trials.

That changed later in 2002 with publication of two randomized trials comparing transarterial therapies to supportive care. The first was a study of 80 patients, the majority of whom had underlying hepatitis B, by Lo[10] et al of transarterial chemoembolization (TACE) using an emulsion of cisplatin and Lipiodol (Lipiodol Ultrafluide, Guerbet, Aulnay-Sous-Bois, France) with gelatin sponge particles with survival as the primary endpoint[10]. There were 40 patients in each group; the TACE group received a total of 192 courses of embolization, median 4.5 per patient. TACE was associated with a

significantly better actuarial survival of 57, 31 and 26% at 1, 2 and 3 years compared to 32, 11, and 3% in the control group. Later that same month Llovet et al[11] published a randomized trial with 3 arms: chemoembolization with doxorubicin, lipiodol & gelatin sponge, gelatin sponge alone and best supportive care. Again, the primary endpoint was survival; response was a secondary endpoint. The study design was sequential; patients were assessed every 3 months and the trial was stopped when a significant survival advantage was demonstrated for the chemoembolization group. At the time the study was stopped the z value of the sequential triangular test for the embolization group remained within the triangular boundaries, indicating the need to recruit additional patients to achieve a valid conclusion. Survival probabilities at 1 and 2 years were 75% and 50% for embolization, 82% and 63% for chemoembolization, and 63% and 27% for symptomatic treatment. Although the authors believe that chemoembolization leads to a survival benefit compared to embolization alone, this could not be concluded statistically because the study was stopped before such a benefit could be demonstrated or refuted. Additional patients would have needed to be recruited into the embolization arm in order to reach a valid conclusion with regard to the impact of embolization vs symptomatic treatment. Of interest, 30 patients treated achieved an objective response by imaging, 16 were in the embolization group, despite the fact that only 35 patients in that group were treated, the other 14 were among the 40 patients treated with chemoembolization. Although this study provided level 1 statistical evidence that chemoembolization offers a survival benefit compared to symptomatic treatment, it did not allow for any statement regarding embolization alone.

That same year Camma et al[12] published a meta-analysis of randomized chemoembolization trials. There were 18 randomized controlled trials pooled for analysis. The authors concluded that "chemoembolization significantly reduced the overall 2-year mortality rate (OR, 0.54; 95% CI 0.33, 0.89; p=. 015) compared with non-active treatment…overall mortality was significantly lower in patients treated with transarterial embolization (TAE) than in those treated with transarterial chemotherapy (OR, 0.72; 95% CI 0.53, 0.98, p=0.39) …..and that there is no evidence that transarterial chemoembolization is more effective than TAE (odds ratio 1.007; 95% CI 0.79, 1.27; P=.95), which suggests that the addition of an anti-cancer drug did not improve the therapeutic benefit".

If indeed the primary effect of transarterial treatment is from ischemia rather than a local chemotherapeutic effect it follows that methods that maximize ischemia should be adopted. To that end calibrated microspheres that are capable of occluding intra-tumoral vessels should be employed for hepatic artery embolization (HAE). In a very elegant study using iron oxide labelled Embosphere® Microspheres (Merit Medical, South Jordan, Utah) published in 2008, Lee and colleagues[13] looked at the distribution of 100-300 µm and 300-500 µm spheres and demonstrated that only the smaller size particles penetrated the tumor. The 300-500 µm particles were found outside the tumor both on MR and histologically. This suggests that 100-300 µm particles and smaller should be

used to most effectively occlude intra-tumoral vessels, presuming that this would result in the most pronounced ischemia and resultant coagulation necrosis. In 2008 Maluccio et al[14] described results obtained in 322 patients thus treated at Memorial Sloan-Kettering Cancer Center. Median survival was 21 months with 1, 2, and3 years overall survival of 66%, 46 and 33%. When patients with extra-hepatic disease or portal vein tumor were excluded the overall survival in the 159 patients with liver only disease rose to 84%, 66% and 51% at 1, 2, and 3 years, with a median survival of 40 months. These are some of the best results ever reported for transcatheter treatment of HCC.

In a yet unpublished randomized controlled trial concluded in 2012 at the same institution comparing chemoembolization with doxorubicin loaded drug eluting microspheres with the same microspheres unloaded there was no difference in response to treatment, progression free survival, or overall survival between the 2 groups. Embolization in each group was performed in an identical fashion, the only difference being whether the microsphere was loaded with doxorubicin or unloaded. This certainly calls into question the role of chemotherapy in hepatic artery embolization.

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