Treatment for Unresectable Hepatocellular Carcinoma

Dr. Thomas Leung MD
Comprehensive Oncology Centre
Hong Kong Sanatorium & Hospital

Introduction
Most patients with HCC present in late stages and are not suitable for curative intent treatment. Treatment for unresectable HCC is largely palliative but occasionally, a small proportion of patients can be downstaged to resectable stage and receive surgery afterwards. Criteria for non-surgical treatment are listed below. Those patients who do not meet the criteria are not likely to benefit from treatment.

Criteria to be met before considering non-surgical treatment:
1. Karnofsky Performance Score over 70%
2. Total bilirubin less than 3 times upper limit of normal
3. Either Child’s A or B
4. No gross ascites
5. No liver encephalopathy

The form of non-surgical treatment can be in the form of local ablative treatment (discussed above already), intra-arterial therapy and systemic chemotherapy.

Intra-arterial Therapy
This is indicated for patients with localised disease in the liver without any extra-hepatic spread. Since the hepatic artery might be embolised during the procedure, the main portal vein should be patent before considering intra-arterial treatment.

Transarterial chemoembolisation (TACE) is commonly performed for unresectable HCC. This involves intra-arterial administration of cytotoxic agents together with a targeting agent, lipiodol, follow by temporary arterial embolisation by gel foam or particles. This needs to be repeated once every 4 to 6 weeks until disease progression. Common side effects after TACE are fever, pain and nausea. There were 2 prospective randomised studies that showed prolongation of survival when compared with supportive care. The benefit of TACE is likely in patients with moderate size tumour (less than 10 cm) which is solitary. Multi-focal disease and infiltrative tumours are less responsive to treatment.

The other form of intra-arterial treatment is selective internal radiation treatment (SIRT) with unsealed radioisotopes. There are 2 kinds of SIRT, namely lipiodol-iodine-131 and yttrium-90 microspheres. Both involve treatment through hepatic angiography and are once treatment. Intra-arterial lipiodol-iodine-131 can be used to treat small tumour (less than 5cm), and sometimes even in patients with portal vein thrombosis. Side effects of lipiodol-iodine-131 are minimal. However, due to relatively long half life of iodine-131, hospitalisation is often over one week after treatment. Intra-arterial yttrium-90 microspheres are commonly used to treat large but localised HCC. The treatment requires accurate pre-treatment nuclear medicine simulation study. Those patients with expected good uptake of the isotopes and low extra-hepatic shunting are suitable for the treatment. Side effects of the treatment are pain, fever, radiation gastritis and radiation pneumonitis. Treatment usually requires hospitalisation of a few days. The overall response rate of SIRT is around 30% and median survival is about 9 months. Occasionally, some patients with unresectable disease can be downstaged to resectable stage after SIRT.

Systemic Therapy
Systemic chemotherapy is indicated for patients with extra-hepatic disease or if they are not suitable for intra-arterial therapy or local ablative therapy. HCC has been generally considered to be chemotherapy resistant. Response rates for most single agent chemotherapy are low and durable remission is uncommon. The most commonly used single agents for HCC are the anthracyclines, namely, doxorubicin and 4’-epidoxorubicin. These drugs consistently produce response rates of around 20%. Complete remissions have been described but are seldom lasting. A prospective trial from Hong Kong that randomised 60 patients to receive either doxorubicin or no active treatment reported an increase in survival from a median value of 7.5 weeks for the control arm to 10.6 weeks for the doxorubicin arm. However, in a systematic review of five other randomised trials involving doxorubicin, no significant survival effect of doxorubicin was discernable. The dose-limiting toxicity of doxorubicin is mainly cardiac and bone marrow suppression. Treatment with doxorubicin is relatively contra-indicated in patients with concomitant heart disease and the dosage should be reduced if the liver function is poor (total bilirubin more than 2 times upper limit of normal). Although combination chemotherapy gives rather higher response rates, durable remission or evidence of improvement in survival remains elusive. Most combination chemotherapy regimens include doxorubicin and cisplatin. Although combination chemotherapy seems to have a higher response rate, there has, to date, been no convincing evidence to suggest combination is better than single agent chemotherapy. For both single agent and combination chemotherapy, objective response is commonly partial (>50% regression in the product of...
tumour diameters) and the duration of remission is short. It is also difficult to compare activity among different regimens because most trials have been single armed phase II studies. Different response criteria were also used which make interpretation and comparison of results difficult. In general, even for well-selected patients, the expected objective response rates for various single or combination chemotherapy is around 15-20%. The low response rate of most single agent and combination chemotherapy is not likely to have a significant impact on survival.

Recently, new combination chemotherapy regimen was tested in a phase II setting and the results are encouraging. Two reports in 1999 have described complete pathological remission after combination chemotherapy using two similar combinations\(^\text{11,12}\). Patt et al\(^\text{12}\) used a four-drug systemic intra-arterial combination chemotherapy (cisplatin 80mg/m\(^2\) day 1, recombinant interferon alpha-2b 5MU days 1,3,5, doxorubicin 40mg/m\(^2\) day 1 and 5-fluorouracil 400mg/m\(^2\) days 1-5) and in a case of disseminated HCC, reported resolution of lung metastasis and a major response in the local tumour. This case was subsequently operated on to remove the residual liver lesion and a complete pathological remission was documented histologically. The name “PIAF”, which stands for the four drugs involved, was coined. A phase II study, using the same drug combination but modified to 4 days of cisplatin and 5-FU infusion, was reported by Leung et al in Hong Kong\(^\text{11}\). This study on 50 patients with unresectable HCC reported an objective response of 26% (all partial response) and median survival of 8.9 months. The modified regimen used 4 days infusion of cisplatin and 5-FU and 4 days of consecutive interferon treatment as well. Although the response rate was not high, 9 out of 13 partial responders had their disease rendered operable after chemotherapy. Pathological examination of the resected specimen confirmed complete remission in 4 patients. The same group has recently updated their results and reported 15 cases (including the 9 cases reported earlier) of unresectable HCC that underwent surgical resection for the residual lesion(s) after partial response to PIAF\(^\text{13}\). There were 8 complete pathological remissions out of the 15 cases and, in the remainder over 95% necrosis.

From these reports, there is now strong evidence showing that complete pathological remission is possible after aggressive systemic combination chemotherapy alone, even for large unresectable HCC. Conversion to resectable disease is also possible by systemic chemotherapy so that clinical remission is achievable after combined chemotherapy and surgery. Although the new combination is effective in selected patients, the regimen is moderately toxic. There were 2 deaths out of 50 patients on PIAF due to neutropenic sepsis\(^\text{11}\). Grade 3 or above leucopenia was seen in 34% of patients and thrombocytopenia in 22% as well. From a multivariate analysis of 149 patients with unresectable HCC, it was found that better liver function (lower bilirubin, shorter prothrombin time, higher albumin level) and younger age are significant predictors of a response and longer survival\(^\text{14}\).

References