Combination Therapy of Sorafenib and Transarterial Chemoembolization in Management of Hepatoma

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ABSTRACT

Incidence of hepatocellular carcinoma (HCC) continues to increase in developing countries and rank 5th in male and 7th in female. Main cause being reported is chronic hepatitis B in Asian region. Treatment of choice for HCC is liver resection, however it is oftenly not possible to be performed as the disease has entered advanced stage. Due to the less choice of treatment in HCC, one of the several other alternatives has been considered is transarterial chemoembolization (TACE) which is applied in patients who cannot undergo resection or ablation therapy, failure of therapy. However limitation of TACE is very high recurrence rate of HCC. Sorafenib is an anti-angiogenic medicine approved as first systemic drug in HCC therapy. Several studies stated the benefits of combination therapy of TACE and Sorafenib administration to prevent HCC recurrence. Success rate of this combination therapy reaches control disease rate of 100% based on response evaluation criteria in solid tumors (RECIST) from European Association for the Study of the Liver (EASL).

***Keywords**: TACE, sorafenib, liver cancer, HCC*

ABSTRAK

Insiden dari karsinoma hepatoseluler (KHS) makin meningkat di negara berkembang dan menduduki peringkat ke-5 pada laki-laki dan ke-7 pada perempuan. Di kawasan Asia dilaporkan bahwa penyebab utamanya adalah hepatitis B kronik. Pilihan pengobatan untuk KHS adalah reseksi hati namun sering tidak mampu laksana karena penyakit tersebut sudah memasuki stadium lanjut. Karena kurangnya pilihan terapi pada KHS maka dipikirkan berbagai alternatif lainnya yang salah satunya adalah kemoembolisasi transarterial yang diaplikasikan pada pasien yang tidak dapat menjalani reseksi ataupun terapi ablasi, gagal terapi. Namun kelemahan dari kemoembolisasi transarterial adalah angka rekurensi KHS yang sangat tinggi. Sorafenib merupakan obat anti angiogenik yang diterima sebagai obat sistemik pertama pada terapi KHS. Beberapa penelitian menyebutkan bahwa manfaat kombinasi terapi kemoembolisasi transarterial dengan pemberian Sorafenib dapat mencegah rekurensi KHS. Angka keberhasilan terapi kombinasi ini mencapai angka kontrol penyakit sebesar 100% berdasarkan response evaluation criteria in solid tumors (RECIST) dari European Association for the Study of the Liver (EASL).

***Kata kunci:** kemoembolisasi transarterial, sorafenib, kanker hati, KHS*

INTRODUCTION

Every year hepatocellular carcinoma (HCC) or liver cancer is being diagnosed in more than 500,000 people world wide, including 20,000 among them in USA. Incidence of liver cancer rank 5 in male and 7 in female. Incidence of HCC increases in developing countries. HCC is a complication commonly found in chronic hepatitis patients and rarely occur before the age of 40. HCC associated with hepatitis C virus infection increases rapidly in USA with the incidence increasing up to threefold with survival rate below 12%. However in Asian countries, highest HCC rate may be associated with chronic hepatitis B infection as major risk factor.[1,2]

Standard treatment in HCC is tumor resection and is considered to be potential as curative therapy. However 15% of all resection candidates usually appear with comorbid, such as cirrhosis, liver function disturbance, presence of multiple lesions, and presence of anatomic disturbance in the liver which disrupt resection process. Liver transplantation is another alternative, particularly in patients with decompensated liver cirrhosis; however, due to limited number of donors, this therapy is generally less performed. Sistematically, chemotherapy also has low survival rate and more oftenly causes toxicity to other body organs.[1,3]

Less choice of therapy in HCC reveals several other alternatives, including ablation as radio frequency ablation (RFA), percutaneous ethanol injection (PEI), cryoablation, and transarterial chemoembolization (TACE). The liver vasculature system consists of the hepatic artery and the portal system with hepatic artery acting as the main vasculature (90-100%) for the HCC tissue. Based on this fact, a therapy was thought to use hepatic artery access to overcome tumor with minimal side effects for non-tumor tissue.[1,3]

Main therapy of HCC depends on the size of tumor, liver function, and general performance status of patients. TACE is usually used in HCC cases in patients who cannot undergo resection or ablation therapy, or has ever undergone therapy, but failed. TACE is considered a bridging therapy to overcome patients' current condition in preparation for main therapy, which is transplantation or liver resection. Based on guidelines published by American Association for Study of Liver Disease (AASLD) and European Association for the Study of the Liver (EASL), TACE is recommended as first line non-curative therapy in patients with large size or multifocal HCC who could not undergo surgical therapy.[4]

As for the disadvantages of using TACE as above, TACE procedure includes injecting chemotherapy directly to the tumor lesion and performing occlusion of hepatic artery which then may decrease the tumor mass. However, unexpected event is the occurrence of devascularization effect which will actually increase the expression of proangiogenic and growth factors.[4,5] This will increase angiogenesis in hypoxic tumor due to TACE and explain the weaknesses of TACE associated with tumor recurrence which causes patients need to undergo TACE procedure for 4 to 6 times. In 2007, drug named sorafenib was found; this drug work as inhibitor of angiogenesis process by stopping the work of vascular endothelial growth factor (VEGF). Sorafenib has been accepted as first systemic treatment for advanced stage of HCC and currently has been used in several clinical-base study.[5]

TRANSARTERIAL CHEMOEMBOLIZATION THERAPY

Curative therapy for HCC includes liver resection and transplantation, but this curative option is only applied in the early stage. In advanced stage liver cancer, local or systemic therapy is needed. Though it is so, cancer resection still hold important role in curative therapy of HCC. Nevertheless, recurrence rate of liver canceris very high, though patient has undergone resection therapy. Chemoembolization is a technique which combine intra-arterial chemotherapy to induce local ischemia in the tumor. In palliative setting, this therapy has shown quite good result in decreasing disease progressivity.[5,6,7]

First TACE succeed to be performed was performed by Doyon et al in 1974, where gelatin sponge was used as emboli agent together with anti-cancer agent first initiated by Yamada et al in 1983.[5,8]

Principle of using TACE is based on liver hemorrhage concept, which consists of 2 arteries: hepatic artery which supplies 90% of liver needs and portal system which supplies the rest. Park et al developed atechnique utilizing hepatic artery as target of emboli agent because it was found that embolization in hepatic artery gave benefit in inducing tumor ischemiaand did not disrupt healthy liver tissue circulation, as it was still supplied from portal vein.[9]

Embolization causes tumor necrosis, thus failure of transmembrane pump system in the tumor occurs. This cause more significant uptake of chemotherapy agent by tumor cells. Concentration of chemotherapy agent was found up to 40 times more compared to healthy liver tissue.[5-8]

Agent which is currently being used is lipiodol, a contras made of opium seed oil. This substance selectively binds neovascularization and tumor extravascular space. Reason of this selectivity is still unknown yet. Maximum dose of lipiodol is 15 mL, however principle of lipiodol use is 1 mL/cm tumor.[5,6] Doxorubicin is the most oftenly used chemotherapy agent, usually used single or in combination with cisplatin, mitomycin or 5-FU. Other agents which can be used are streptozocin, vinblastine and gemcitabine. There is still no research stating the superiority of each agents.[4,5]

Barcelona Clinic Liver Cancer, in its guidelines, recommends the use of TACE in intermediate stage of HCC (OKUDA 1-2, performance score 0 and large or multinoduler cancer), and in particular patients with advanced stage HCC (OKUDA 1-2, performance score 1 and no extrahepatic metastasis of HCC).[1,5,7]

Although there is no absolute contraindication of TACE, there are several conditions in which TACE could not be performed, which is massive tumor or which infiltrate upto 50% of liver tissue, liver insufficiency or liver failure, high bilirubin level (more than 5 mg/dL), A-fetoprotein level more than 1,000 ng/mL and high LDH level (more than 425 IU/L), and transaminase level more than100 IU/L. Contraindication of chemotherapy agent and embolization is the presence of allergy or anafilaxis reaction history towards the agent. Condition, in which occlusion has happened in portal system hemorrhage, is also thought to disturb the continuance of healthy liver tissue if TACE is still continued.[1,5,7]

SORAFENIB THERAPY

Hepatocarcinogenesisis multifactorial process where a stimulus may change the genetic system in hepatocytes, leads to cell proliferation and death. Genetic changes could be accumulated in conditions, such as chronic hepatitis and cirrhosis in which recurrent destruction and hepatocyte regeneration occurred in short time to create hepatocyte cells with defects. These defects include mutation in gene p73, p53, Rb, APC, DLC-1 (deleted in liver cancer), p16, PTEN, IGF-2, BRCA2, SOCS-1, Smad2 and Smad 4. Cell proliferation is marked by the presence of vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGFR) molecule secretion, inducing the occurrence of cell and endothelial cell proliferation for tumor tissue neovascularization.

Presence of hypoxic condition in tissues initiates binding of growth factor with receptor located in the cell target membrane. This causes phosphorilation of this receptor in continuing signal through Ras protein to Raf kinase which is then further relayed by MAPK kinase (MEK) and extracellular-signal regulated kinase (ERK). This activation of ERK component promotes angiogenesis process.[4,10-12]

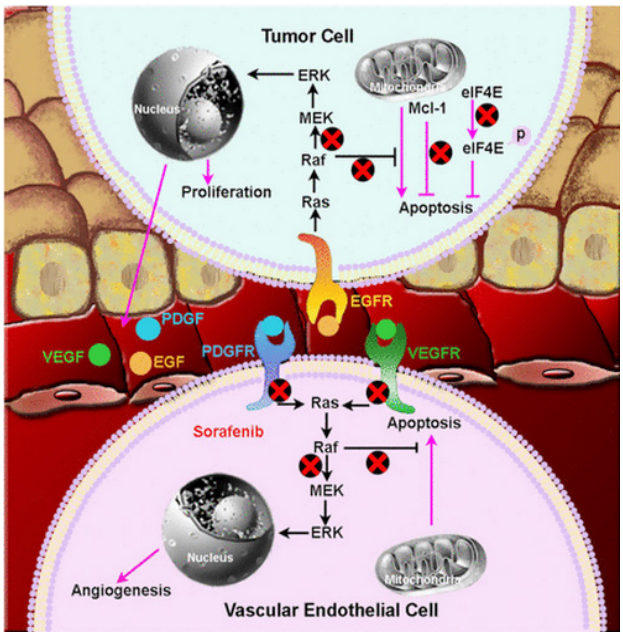

Figure 1. Angiogenesis process which is promoted by the activation of extracellular-signal regulated kinase[4,10-12]

Therapy option for advanced stage liver cancer is very limited, but because of study and recognition of growth factors, Sorafenib or also known as BAY 43-9006 was found, which acts by disrupting MAPK signal pathway by holding membrane receptors, especially tyrosine kinase activity and relaying signal from RAF. Kinase receptors mentioned above are receptors for VEGF, PDGF, c-KIT receptor and RET receptors. These kinasesreally play role in proliferation and endothelial cell migration which is a part of tumor cell angiogenesis.[11-14]

Anti tumor effect from sorafenib is found to be dose-dependent when evaluated in rat model. Decreased angiogenesis rate was found to be 49% in 10 mg/kg dose and even 30 mg/kg dose managed to inhibit tumor growth by 100% for 21 days. In human clinical trials, it was found that oral dose of 400 mg administered every 12 hours for 4 weeks has increased survival rate up to 9.2 months with median decrease of tumor growth progressivity for 4.2 months. Phase III study in human has been performed, and in study of heart and renal protection (SHARP) from March 2005 to April 2006, it was found that there was no difference in tumor progression in sorafenib group compared to

the placebo group. Similar study conducted in Brazil, a restrospective study, it was found that there were a lot of side effects which required lowering sorafenib dosage. Side effects meant above were diarrhea, hand-foot syndrome, itchiness.[15] However it was also mentioned that these side effect were managable and in the study, 11% patients had to stop from the study due to serious side effects.[11-14]

This phase III trial also has its own bias factors, such as including subjects from Asia Pacific region with higher occurence of advanced stage of liver cancer, therefore the obtained effectivity rate of sorafenib was lower. Therefore, to obtain better effectivity rate, it was thought to combine 2 therapy modality, which are TACE and Sorafenib which both has the principle of decreasing tumor size by inducing hypoxia; the logic in sorafenib administration in this concept was to prevent neovascularization for tumor cells after embolization and chemotherapy agent administration into tumor cells.[11-14]

COMBINATION OF TACE AND SORAFENIB

Management criteria in liver cancer (HCC) is based on the classification made by Barcelona Clinic Liver Cancer (BCLC) which divides patients into 5 categories: 0, A, B, C, and D based on prognosis variable and the available choice of therapy. Based on this guideline, therapy option TACE and Sorafenib each is located in category B and C, whereas category D is categorized in palliative therapy. Based on this guidelines, TACE is performed with the purpose of decreasing neoplasm mass in the liver to decrease the stage, so patient may undergo curative therapy, tumor tissue resection. Nonetheless, this is rare to be achieved due to the hypoxic effect after TACE which induce angiogenesis cascade as has been discussed previously. Based on this concept, it was thought to use combination therapy of TACE and Sorafenib to inhibit angiogenesis reaction with Sorafenib systemic therapy.[7]

In SHARP study by Llovet et al, it was found that Sorafenib, inhibitor of VEGF and Raf kinase, was able to increase survival of patients with advanced stage liver cancer. Recent study using sorafenib in combination with TACE has shown significant result. Ferrel et al used conventional TACE procedure followed by sorafenib treatment and showed that this postponed cancer progressivity significantly in intermediate stage of HCC associated with HCV, without unexpected adverse effects.[6,12]

Pawlik et al conducted a phase II single arm study in 2011, a single-center prospective design to evaluate safety and effectivity in sorafenib use which was

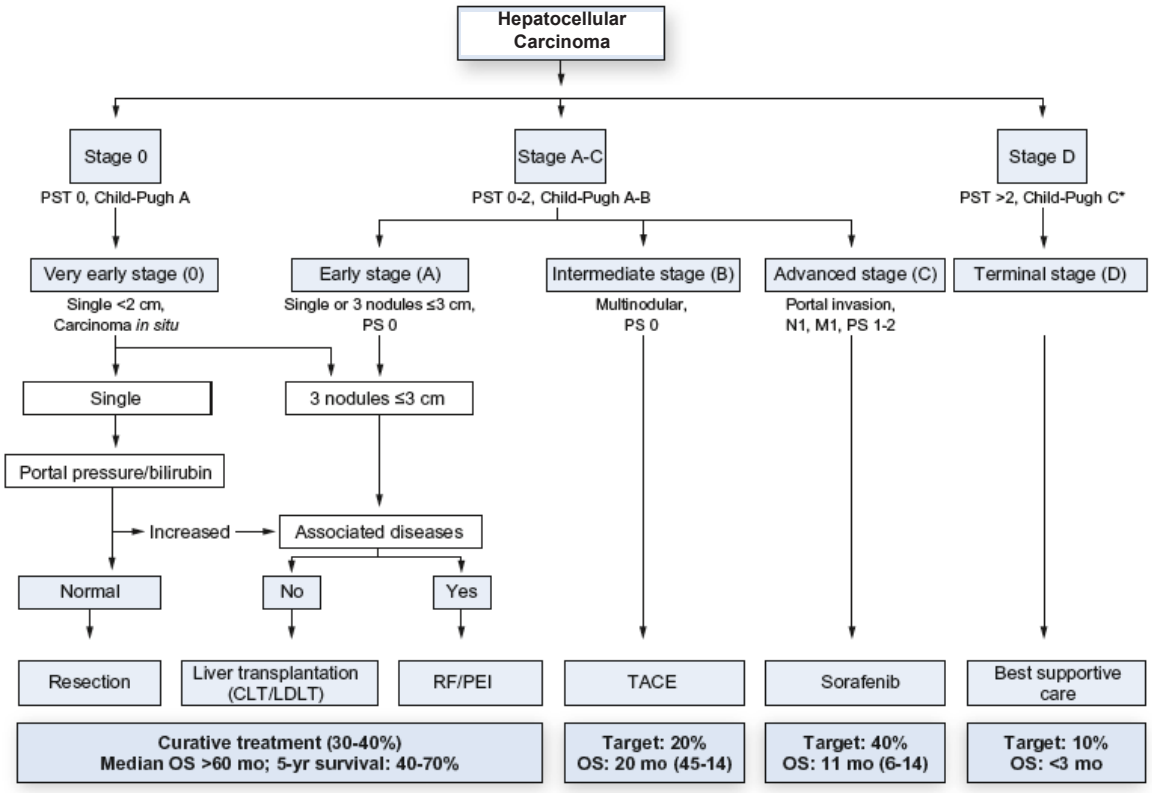

Figure 2. Management criteria in liver cancer based on classification made by Barcelona clinic liver cancer[7]

combined with DEB-TACE (TACE + Doxorubicin) in unresectable HCC patients. This study evaluated safety and toxicity in patients who underwent TACE and Sorafenib administration in advanced stage HCC. Secondary final target in this study was evaluating tumor response toward therapy which was accessed using MRI with contras to measure size of target lesion. This result was then matched with response evaluation criteria in solid tumors (RECIST), and contrast uptake degree in magnetic resonance imaging (MRI) based on EASL criteria.[16]

Patient was given regimen for 6 weeks every cycle, in which in the first cycle, only sorafenib was administered (400 mg twice daily administered 1 week before DEB-TACE). Sorafenib was continued in combination with DEB-TACE starting from the second week. Clinical examination was performed every week with laboratory examination in week 3 and 5. Sorafenib dose reduction (400 mg daily or every 2 days) or even treatment interruption was permitted in patients who experienced toxicity. However, if further dose reduction was needed, subjects were excluded from the study. DEB-TACE was given at a maximum dose of 100 mg doxorubicin per procedure.[16]

All patients qualified to participate in this study was given 128 cycle of therapy (Sorafenib and DEB-TACE – 60 cycle, and only Sorafenib – 68 cycle). Median of treatment duration was 71 days. In the first week of Sorafenib administration, 91% patients experienced toxicity which includes fatigue in 50%, hand-foot-skin reaction (HSFR) in 30%, rash in 20% and upper right abdominal pain in 18%. Majority toxicity in the first week was included in category stage 1 and 2 (92%) compared to category 3 and 4 (8%). Grade 3 and 4 toxicity being found was increased of lipase enzyme (3%) and encephalopathy (3%). During the first cycle, it was obtained that 30 from total of 33 patients experienced grade 3 or 4 toxicity associated with administration of combination sorafenib and DEB-TACE. However, during cycle 2 administration, it was found that only 15 patients (54%) experienced grade 3 or 4 toxicity. This can be seen in figure 3 in which there is comparison of toxicity in the first week with sorafenib alone, combination of sorafenib and DEB-TACE in the first cycle, also toxicity cummulative calculation during the study.[16]

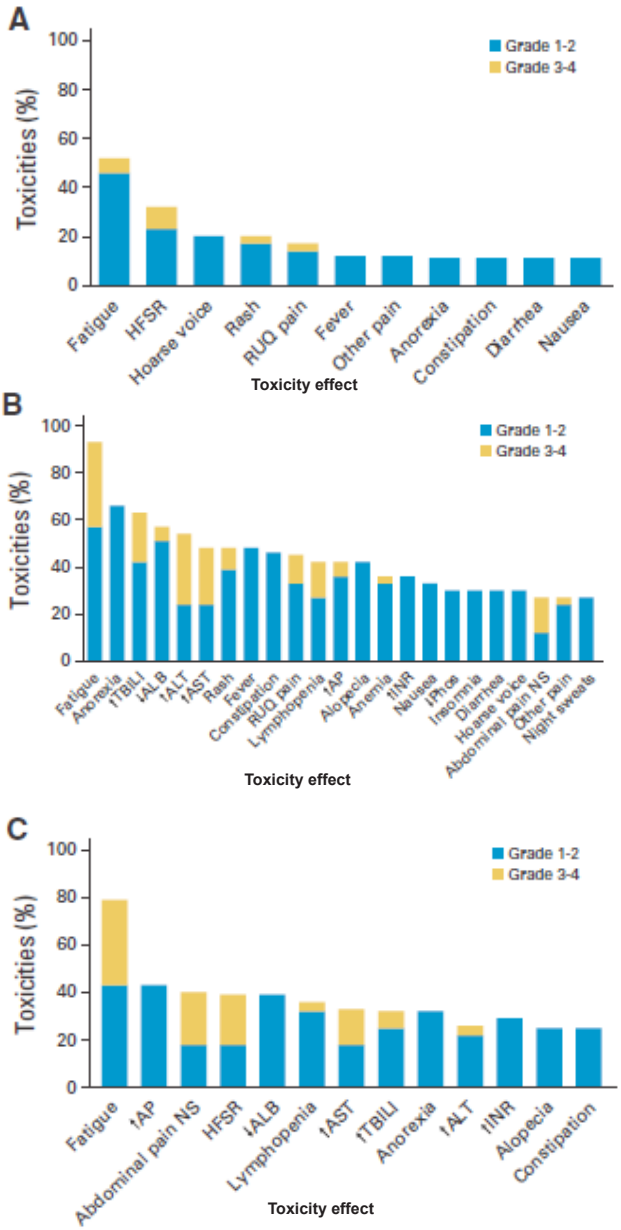

Figure 3. Comparison of toxicity in the use of Sorafenib in: (A) A week before TACE; (B) First cycle Sorafenib and TACE; (C) Cummulative rate incidence of toxicity during the study[16]

Result of study also showed that toxicity degree was the same in the second cycle of treatment; this was proved by the incidence 15 patients from 28 patients experienced upto grade 3 or 4 toxicity. From all toxicity being reported, percentages of grade 3 and 4 toxicity incidence from first and second cycle were 17% and 16%, respectively. Figure 4 also showed comparison of liver function on study initiation and during treatment. Patient who received sorafenib administration before and after DEB-TACE had lower bilirubin level compared to patients without sorafenib administration (median 0.87 mg/dL vs. median 1.5 mg/dL). Patients with base of high bilirubin level (> 2 mg/dL) had higher bilirubin level and lower albumin level

compared to patients with base of normal bilirubin level even after DEB-TACE (total bilirubin 5.84 vs. 0.96 mg/dL, albumin 2.9 vs. 3.4 mg/dL).[16]

From effectivity point of view, after one cycle of sorafenib and DEB-TACE, it was found that there was 4% decrease in tumor size (from 6.0 cm to 5.8 cm). Treatment response was evaluated based on RECIST criteria from EASL with response rate of 58% and disease control rate of 100%.[16] This study showed that the use of combination sorafenib and DEB-TACE in advanced stage HCC patients was safe and well-tolerated by patients. This toxicity could be overcome by adjusting sorafenib dose which showed quite good response. Result of initial study showed that effectivity of DEB-TACE in combination with sorafenib revealed good success rate based on RECIST criteria from EASL. Data obtained in this study was expected to give picture on safety and effectivity of Sorafenib and DEB-TACE which could be areference for other big studies, such as Sorafenib or placebo in combination with TACE (SPACE) and Eastern cooperative oncology group (ECOG).[16]

Nonetheless, a study by Kudo et al also assessed efficacy and safety from sorafenib administration towards response in TACE administration in Korean and Japanese individuals experiencing unresectable HCC. This study concluded sorafenib did not give significant result in extending time for progressivity or survival rate; however, the median exhibited that progressivity occurs about 2 months later compared to the placebo group. Many factors contributed as causes, such as: high number of patients upto 73% needed reduction of sorafenib dose and 91% experienced drug interruption. Thus sorafenib dose needed to be given was 386 mg, while for the adverse effects of sorafenib in combination with TACE, high result was obtained. Therefore, it was adviced to start sorafenib administration with low dose or time adjustment of sorafenib administration with TACE, so it would be well-tolerated by individuals until sinergistic effects occurred.[14]

CONCLUSION

Combination of sorafenib and DEB-TACE use in advanced stage HCC patients was well-tolerated by patients. Toxicity could be overcame by adjusting sorafenib dose, which showed good response. Effectivity of DEB-TACE in combination with sorafenib proved high success rate based on RECIST criteria from EASL. Further study on proper administration of sorafenib dose is still needed. This study recommended starting sorafenib treatment with low dose, which is then increased gradually while monitoring signs of toxicity.

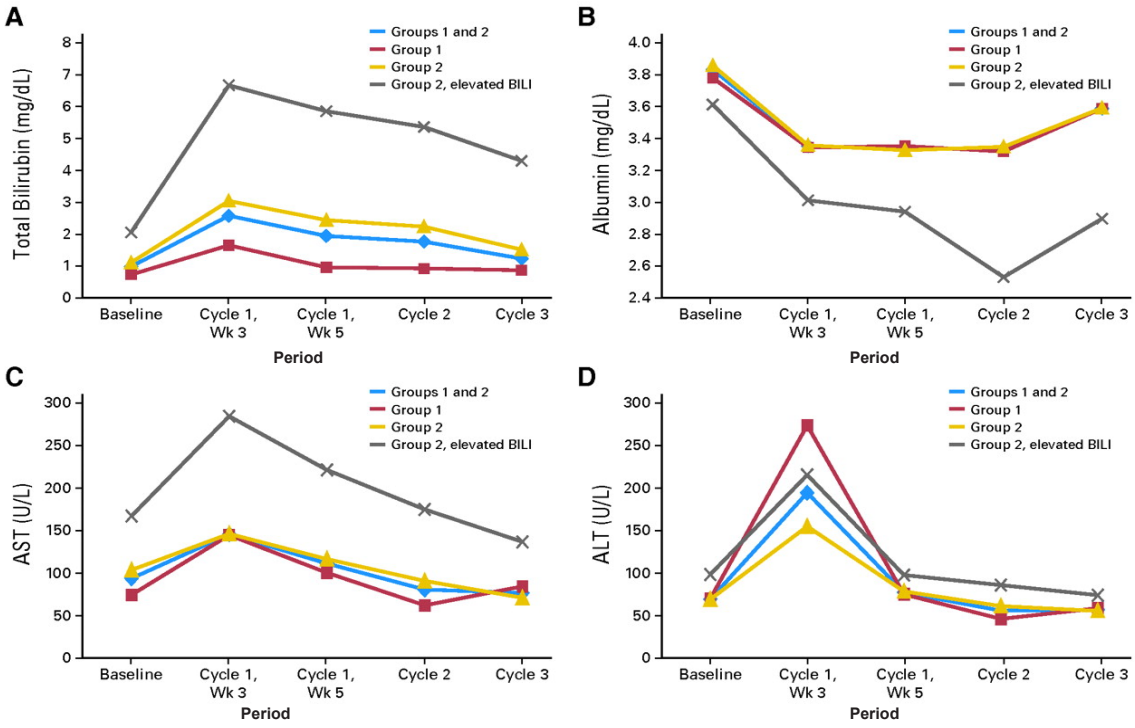

Figure 4. Graph of bilirubin level (A), albumin (B), AST (C), and ALT (D) during the study from the initial level until the end of cycle 3[16]

Currently, the most effective therapy in liver cancer management is TACE or Sorafenib based on its disease stage. Currently, combination therapy which can be used with TACE is Sorafenib, however, further studies are still needed to confirm this result. Lately, study is performed based on reference time to progression or progression free survival. However, based on AASLD and EASL, the best reference is time to progression because it is more valid and is able to picture the effectivity of a particular therapy holistically.

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