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Cancer Science 2019 - Stereotactic body radiotherapy in liver metastasis - Neeraj Jain - Sri Guru Ram Das University of Health Sciences and Research

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To evaluate the effect and mechanism of radiotherapy (RT)-sorafenib pharmacokinetics (PK) in different regimens with conventional or high dose irradiation. Between February 2012 and December 2018, 43 patients with portal vein tumor thrombosis treated with sorafenib plus conventional RT (58%) or stereotactic body radiation therapy (SBRT, 42%) were retrospectively reviewed. In vivo and in vitro studies of concurrent and sequential RT with sorafenib were designed. SBRT resulted in a 3-fold increase in complete recanalization compared to conventional RT group (28% vs. 8%, $p = 0.014$). Compared to the control group, the area under the concentration vs. time curve (AUC) of sorafenib was increased in the concurrent RT2Gy and RT9Gy groups and the sequential RT9Gy group by 132% ($p = 0.046$), 163% ($p = 0.038$) and 102% ($p = 0.018$), respectively; and was decreased by 59% in the sequential RT2Gy group ($p = 0.036$). Sequential RT2Gy and RT9Gy increased CYP3A4 activity by 82% ($p = 0.028$) and 203% ($p = 0.0004$), respectively, compared to that with the corresponding concurrent regimen. SBRT produced better recanalization than conventional RT with sorafenib. The AUC of sorafenib was modulated by RT. P-gp expression was not influenced by RT. The sequential RT regimen increased CYP3A4 activity that may increase the RT-sorafenib synergy effect and overall sorafenib activity. The biodistribution of sorafenib was modulated by local RT with the different regimens. Hepatocellular carcinoma (HCC) is one of the most prevalent solid tumors worldwide1. Less than 30% of patients are eligible for curative treatments, and most are incurable. Stereotactic body radiation therapy (SBRT) is an alternative treatment to ablation/embolization techniques or can be used when these techniques either fail or are contraindicated for HCC. Additionally, SBRT exhibits a dose-response relationship for local control and overall survival in HCC patients. Sorafenib (Nexavar, Bayer Pharma AG, Berlin, Germany) is an oral multikinase inhibitor that targets the Raf/mitogen-activated protein kinase (MAPK)/extracellular-signal-regulated kinase (ERK) signaling pathway to induce tumor cell apoptosis in HCC.

The combination of oral sorafenib with RT or SBRT may exhibit synergy for inhibiting tumor growth. However, toxicity of the SBRT-sorafenib combination for HCC with a high effective volume of irradiated liver has been noted. Recently, RT has been shown to modulate the systemic pharmacokinetics (PK) of anticancer drugs and affect the composition of the microenvironment. These lines of evidence suggest that interactions between sorafenib and RT may modulate the PK of sorafenib. However, the time schedule and dose of RT for use in combination with sorafenib are controversial.

The present study was designed to evaluate the possible mechanism of the RT- PK of sorafenib with different time schedules and doses in both in vitro and in vivo studies and assess the clinical response to provide suggestions for clinical applications. The liver is a common site of metastatic disease from some of the most prevalent malignancies, in particular gastrointestinal tumors for which metastatic deposits travel through the portal venous system. Approximately one-third of patients with solid tumors will develop liver metastases. In a large autopsy series the prevalence of liver involvement was 86 % for pancreatic cancer, 60% for breast cancer, and 42% in colorectal cancer. The liver is a common site of metastatic disease from some of the most prevalent malignancies, in particular gastrointestinal tumors for which metastatic deposits travel through the portal venous system. Approximately one-third of patients with solid tumors will develop liver metastases. In a large autopsy series the prevalence of liver involvement was 86% for pancreatic cancer, 60% for breast cancer, and 42% in colorectal cancer. Hepatic involvement is often life-limiting and can result in severe morbidity. Approximately half of metastatic deaths from breast and prostate cancers are associated with liver metastases. Death due to colorectal cancer is frequently related to liver metastases, often as the only site of metastatic disease. Systemic therapy is usually the primary therapy for metastatic liver disease, as it may allow for transitory responses and increased median survival. For patients with metastatic colorectal cancer treated with current palliative chemotherapy, median survival now approaches two years. Although whole liver radiotherapy has long been abandoned as an anti-cancer therapy, current (infrequent) use in symptomatic patients may still offer symptomatic relief.

The goal of aggressive local treatment is long-term disease control for selected patients. Its benefits are now supported by large retrospective series. With a long history, surgical resection remains the gold standard local treatment of hepatic metastases-typically of colorectal origin. Surgery is associated with an acute risk of death (typically in less than 5 %) but can lead to five-year overall survival rates of up to 58 %. When Wilson and Adson retrospectively analyzed patients with limited liver metastases of colorectal cancer, approximately one-quarter of the resected patients were alive at five years. All long-term survivors in this series had solitary metastases, while none of the patients with multiple metastases or comparable non-resected patients were alive at five years.14 Adson et al. reported similar results, with 25 % five-year survival rate for resected patients versus 2.5 % in a non-resected group.

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Fong et al. studied 456 consecutive patients with liver metastases of colorectal cancer resections. They reported a 38 % five-year survival rate with a median survival of 46 months. Despite the apparent benefits of surgery, clinical and technical limitations narrow eligibility to metastasectomy. Limitations may relate to: location of the metastases; surgical plans unable to preserve sufficient liver parenchyma; medical comorbidities; or patient refusal. Thus only 10-25 % of patients with liver metastases from colorectal cancer can benefit from curative resection. New therapeutic options enable radical treatment instead of, or in combination with, surgery. Minimally invasive thermo-ablative procedures such as radiofrequency ablation (RFA), microwave ablation, cryotherapy, or laser-induced thermo-therapy have been developed. Complementing and competing with these is stereotactic body radiotherapy (SBRT)- a novel non-invasive approach with particular benefits: it can spare large vessels and, not being a thermal therapy, is insensitive to their cooling effects.