Combined Use of Regorafenib with SBRT in Pulmonary Metastasis from Colorectal Cancer

Použití regorafenibu a SBRT při léčbě plicních metastáz kolorektálního karcinomu

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Colorectal cancer is the third most common cancer in humans. Metastases are the main cause of death in colorectal cancer patients. The most common areas of metastases include liver, lungs and peritoneum. Lung metastasis will develop in approximately 2–54% of patients with colorectal cancer during the course of the disease. When left untreated, prognosis is poor in metastatic cases with median survival time of 5–9 months [1–3].

In colorectal cancer cases in which the primary tumor is under control, curative therapies are attempted due to prolonged life expectancy in patients with single oligometastasis confined to the lung, and surgical resection of pulmonary lesion is the first choice. Stereotactic body radiotherapy (SBRT) has been increasingly used in the management of oligometastasis in case of the patient's refusal to surgery, comorbid conditions or in patients who are ineligible to surgery due to vital risks, which is a non-invasive treatment modality as effective as surgery but one that does not harbor potential complications of surgery [2,3]. SBRT is a non-invasive treatment modality delivering high dose radiotherapy per fraction, which aims to deliver high dose radiotherapy to target tissue while providing maximum protection to adjacent tissues. In recent years, SBRT was introduced into routine practice as a more invasive treatment where respiratory movements are minimized by advanced imaging methods. In colorectal cancer, results of current studies on SBRT in patients with pulmonary metastasis showed that this treatment modality is a safe and tolerable method which may be performed on an outpatient basis [2–4]. Recent studies show that local control of the tumor can be improved by increasing radiotherapy doses in lung metastasis. In general, SBRT is given at doses of 60 Gy/3–8 fractions (biological effective dose 105–180 Gy) [3,4]. In previous studies,1-, 2- and 5-year overall survival rates were reported as 83–100%, 43–76% and 39–49%, resp., in pulmonary metastasis from colorectal cancers. In addition, minimum toxicity was reported for SBRT [4,5]. In a review on metastatic colorectal cancer patients, Wild et al. reported 1-year local control rate as 77–100% and grade 3 or higher toxicity rate as less than 10% in SBRT when used in lung metastasis [4]. Today, a few prospective studies are completed and many are ongoing.

In recent years, there was an increase in the effectiveness of regorafenib, which is introduced as targeted agent in metastatic colorectal cancer, in combination with SBRT, becoming the focus of interest in combination therapies due to high response rates. However, studies are limited to case reports, and there is no retrospective or prospective study on this issue [3,6]. Regorafenib is an oral tyrosine kinase inhibitor approved for metastatic colorectal cancer by U. S. Food and Drug Administration in 2012. It exerts anti-angiogenic properties through vascular endothelial growth factor 1–3 (VEGF1–3) and tunica interna endothelial 2 (TIE-2) inhibition, stromal signal inhibition through platelet-derived growth factor receptor ß (PDGFR-ß) and fibroblast growth factor receptor (FGFR) inhibition and antioncogenic features through tyrosine-protein kinase (KIT), PDGFR and receptor tyrosine kinase (RET) inhibition [1,3,6,7]. In a placebo-controlled phase II study, it was reported that regorafenib showed significant improvements in overall survival, disease-free survival and disease control [7]. In another study,

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Roberto et al. investigated effectiveness and safety of SBRT plus regorafenib combination therapy in patients with pulmonary metastasis of colorectal cancer. The authors emphasized that regorafenib improved disease control and survival and that regorafenib used in combination with SBRT was safe and effective. In addition, regorafenib use is not contraindicated even in patients with disease progression [3]. Gatto et al. used regorafenib plus SBRT combination in 2 patients with metastatic gastrointestinal stromal tumor and achieved local tumor control in one patient while objective response in the other patient [6].

In conclusion, existence of metastases from colorectal cancers, particularly pulmonary metastasis, is important for determining treatment approach. In this group of patients, local ablative approaches (such as SBRT) are widely used in addition to systemic therapies. Today, SBRT to metastases is planned to prolong disease-free survival or to achieve cure as reported previously. It seems that targeted agents, such as regorafenib, combined with SBRT may provide higher clinical benefit in these patients. Thus, it is of important to identify patients that may benefit from these therapies.

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