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Cover Story

Enhanced treatment of lung cancer by metronomic therapy with oral pemetrexed

Metronomic chemotherapy is a new regimen of drug administration involving frequent administrations of conventional chemotherapeutic agents at very low doses to minimize adverse effects and a rare chance of developing acquired drug resistance [1]. It mainly targets activated endothelial cells in tumor vasculature, consequently inhibiting angiogenesis, while revitalizing immune cells in the tumor microenvironment and directing cytotoxic effects to tumor colonies [2]. Conventional chemotherapy depends on the maximum tolerated dose therapy, which often leads to off target tissue distributions with prolonged drug-free periods that help to develop chemo-resistant tumor cells and eventually cause cancer relapse. In contrast, chemotherapy with a metronomic protocol is given at reduced doses in regular intervals and draws high anti-cancer efficacy by continuously maintaining a low drug concentration [3].

Instead of dumping the maximum tolerated dose into the body to kill tumor cells, the same drug in the metronomic chemotherapy schedule demonstrates various dose-dependent anticancer efficacy by preferentially inhibiting circulatory endothelial cells, angiogenesis, T-regulatory cells, as well as cancer stem cells [4]. In particular, a potential metronomic chemotherapy regimen may provide cancer patients the opportunity to delay tumor progression during the maintenance treatment. Currently, the U.S. Food and Drug Administration (FDA) has approved Pemetrexed as a single agent for long-term maintenance therapy in non-small cell lung cancer; however, the intravenous administration of the drug is not suitable for metronomic settings because of the adverse reactions associated with high doses and the concerns about patient's discomfort due to frequent drug administrations. Thus, the current challenge in using Pemetrexed for the long-term treatment of lung cancer is to circumvent the intravenous administration in the clinic.

The article by Professor Byun and his colleagues in this issue explored the possibility of metronomic chemotherapy using Pemetrexed via oral delivery for the treatment of non-small cell lung cancer [5]. The orally active Pemetrexed was formulated by physically mixing with the bile-acid derivative (deoxycholyl-L-lysyl-methylester or DCK) as an oral absorption enhancer. The oral Pemetrexed/DCK complex significantly increased the absorption of Pemetrexed through both transcellular transport and bile-acid transporter mediated absorption. This result indicates that Pemetrexed/DCK complex may escape from the efflux transporter, which is capable of limiting oral absorption of various anticancer drugs. Pharmacokinetics (PK) studies show that the proposed formulation enhanced oral bioavailability and overall PK parameters in rats. The orally active Pemetrexed/DCK complex suppressed tumor progression in a dose-dependent manner in the murine squamous carcinoma SCC7 xenograft model. Moreover, the combination of orally administered Pemetrexed/DCK complex in low-doses with cisplatin showed superior anticancer effects in the A549 lung cancer xenograft model. Daily administered pemetrexed/DCK complex reduced tumor progression and enhanced tumor tissue apoptosis. In contrast to intravenously administered Pemetrexed, the proposed metronomic chemotherapy affects tumor endothelial cells, thereby reducing angiogenesis in A549 tumor tissue. In addition, the oral Pemetrexed/DCK complex reduced tumor cell proliferation through upregulating the plasma deoxyuridine by targeting the folate dependent enzymes. The findings reveal that this oral formulation has minimal local and systemic adverse effects in mice.

The study by the Byun team demonstrates the efficacy of oral metronomic chemotherapy in two xenograft models. The efficacy demonstrated in animal xenograft models, however, has been a poor indicator of the promising therapeutic effects in clinical studies. Thus, there is a compelling need to carefully design a suitable animal model or *in vitro* models that can mimic the actual *in vivo* condition in humans. At the same time, we can expect more positive outcomes in clinical studies with metronomic chemotherapy, as it is often combined with other anti-angiogenic standard treatments because of the administration of low doses. In the work by the Byun team, metronomic pemetrexed was used in combination with cisplatin to show synergistic pharmacological response. The oral pemetrexed administration at low doses allows a non-toxic individualized dosing strategy while maintaining effective drug concentration in the metronomic settings. If the metronomic chemotherapy with dual-drug administration shows a potential clinical efficacy, then multi-drug metronomic chemotherapy can also be developed. Since the metronomic chemotherapy approach is not based on delivery of the lethal drug dose to target tumors, the multi-drug metronomic chemotherapy approach is expected to be different from previous tumor-targeted delivery of nanomedicines. The development of an anticancer drug oral formulation provides a new, exciting opportunity for existing anticancer drugs to be used more frequently and in combinations for a long-term maintenance therapy.

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