Clinico-pharmacological study of low dose capecitabine and oxaliplatin versus standard XELOXin metastatic colorectal cancer

Thesis

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Summary

Despite advances in screening and treatment, colorectalcancer (CRC) remains the fourth-leading cause of cancerrelateddeath and is responsible for approximately 50,000deaths each year in the United States alone. Depending uponthe stage of disease, CRC treatment caninvolve multiplemodalities including surgery, radiotherapy,interventionalradiology approaches and systemic chemotherapy.

Surgical intervention alone is curative in many patientswith early-stage disease. For patients with locally advanceddisease (stage III), adjuvant 5-fluorouracil (5-FU)-based chemotherapysignificantly enhances the relapse-free survival.

In the metastatic setting, the current standard first-linechemotherapeutic options for patients with metastatic

CRCare 5-FU in combination with leucovorin and either oxaliplatin(FOLFOX) or irinotecan (FOLFIRI). These treatments haveincreased median survival from 10 to 14 months with 5-FUand leucovorin alone to 16 to 23 months with FOLFOX andFOLFIRI. This survival increased to 29 months with the use of biological agents.

Colorectal cancer is one of a few cancers in which definitive treatments foroligometastatic disease can still be cured with definitivetreatment, thereby increasing the rates of hepatic ablations and metastasectomies which requires the need for multiple disciplines to be involved in the care of these patients. In addition, the use of molecular analyses for subtypingCRC is becoming more common practice, especially in themetastatic setting.

Conventional chemotherapyCHT is normally administered near the maximal tolerateddose (MTD), typically in 3-week cycles. CHT is usedin this way with a 3 or more weeks' drug-free period. During thedrug-free period, regrowth of parts of the cancer cellsoccurs, especially if the drug-free period is too long.Metronomic chemotherapy refers to the frequent,even daily, administration of chemotherapeuticsat doses significantly less than the maximumtolerateddose, with no prolonged drug-free breaks.

The study included 70 patients diagnosed with chronic

phase metastatic CRC admitted to NCI between years of 2016-2018. Statistical analysis was done to test if low dose capecitabine and oxaliplatin were as good as classic XELOX regarding PFS at 2 years with less toxicity. In addition to pharmacological study of capecitabine pharmacokinetics and genetics in both protocols.

The median duration of the treatment for each arm was 6 months. Toxicity occurred in 26 cases (75 % of arm A) and 21 cases (60% of arm B), The median TTP for patients receiving arm A was 7.6 months while the patients receiving arm B had median TTP 5.7 months (P=0.318) while the median OS for Arm A (15.9) and for Arm B (15.8) (p=0.8) that is insignificant.

Anemia, diarrhea, hand & foot syndrome, neutropenia, oral mucositis, fatigue, gastritis and abdominal pain were significantly higher in group A than group B (P-values: 0.03, 0.027, 0.002, 0.001, 0.003, 0.03, 0.004, 0.048). Most of grade III toxicities were significantly recorded in arm A whereas a smaller proportion of them recorded in arm B. The significant recorded grade III toxicities were anemia, hand and foot syndrome, neuropathy, fatigue, gastritis and abdominal pain (P-values: 0.017, <0.001, <0.001, <0.001, <0.0001, 0.019) respectively.

Metronomic protocol was associated with lower rates of toxicity with nearly equal improvement in PFS or OS than standard protocol.

Its suggested based on this small sized study to initiate large size one to test concept of metronomic chemotherapy in faire patients or those with limited performance status versus standard chemotherapy which should include age related quality of life and toxicity management.