ATTEMPTS AT IMPROVING FLUOROPYRIMIDINE CHEMOTHERAPY BY BIOCHEMICAL MODULATORS OR BY BIOMARKER MEASUREMENTS WITH LASER SCANNING CYTOMETRY

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To study the possibilities for the improvement of the efficacy of fluoropyrimidine chemotherapy (i) we characterized the effect of biochemical modulators – leucovorin (LV), uridine (U) or uridine-diphosphoglucose (UDPG) and 5-ethyl-2'-deoxyuridine (EDU) on the myelotoxicity of 5-fluorouracil (5-FU) in mice by estimating the cellularity and CFU-GM-content (granulocyte-macrophage progenitor cell) in the bone marrow as well as neutrophil counts in the blood and (ii) investigated the capabilities of laser scanning cytometry (LSC) for the possible prediction of patients' response to fluoropyrimidine therapy by the quantitative measurement of the ratio of thymidine phosphorylase (TP) and dihydropyrimidine dehydrogenase (DPD) in tissue sections. Additionally, the sensitivity of LSC in detecting GFP transfected cells was determined with the purpose to study the early stages of metastasis development.

U given after LV+5-FU significantly reduced the severe myelotoxicity of this combination and UDPG, a prodrug of U with a better safety profile, produced similar beneficial effects. Granulocyte colony stimulating factor (G-CSF) improved the recovery from neutropenia after LV+5-FU and the combination of U (or UDPG) and G-CSF was more effective than either U or G-CSF alone. Explanation: U potentiated the beneficial effect of G-CSF by increasing the number of progenitor cells surviving LV+5-FU. These results warrant further studies and may contribute to the more effective clinical use of LV+5-FU. EDU increased the myelotoxicity of 5-FU, especially with a fractionated 5-FU dosing, suggesting that this effect was mainly due to delaying the recovery of myeloid progenitor cells. This should be considered in possible future clinical studies.

We found that the phantom contouring feature of the LSC is applicable for the direct quantitative measurement of TP/DPD ratio in tissue sections which warrants further retrospective studies with archived material to determine its potential for individualized therapy. We determined that the sensitivity of the LSC in detecting GFP positive cells (~$1:10^4$) is promising with respect to the in situ analysis of the homing of tumor cells.