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Editorial

Adjuvant 5-FU based chemotherapy for colon cancer: Match or miss the mismatch?

Mismatch repair recognises base–base mismatches and insertion/deletion loops and thus it is essential for maintaining the fidelity of DNA replication.[1] The deficiency of DNA mismatch repair due to mutations of the proteins involved in this mechanism predisposes to cancer and is responsible for mutator phenotype. Laboratory studies have indicated that mismatch repair deficiency confers resistance to several anticancer drugs, including cisplatin, methylating agents and some antimetabolites. A significant proportion of intestinal cancers, approximately 10–15%, are mismatch repair deficient and thus it is certainly pertinent to ask the question whether the anticancer therapies have a different efficacy depending on mismatch repair status.

The paper by Jover et al., published in this issue of EJC,[2] reports the results of a study designed to answer this question in colorectal cancer patients treated with adjuvant chemotherapy with 5-fluorouracil (5-FU).

The data indicate that adjuvant chemotherapy with 5-FU only improved survival in patients with a mismatch repair proficient mechanism, whereas in patients with mismatch repair-deficient tumours, the treatment was ineffective. According to this finding, 5-FU and presumably its analogues should only be given to colorectal cancer patients showing tumour mismatch repair competence, and not to patients with tumours that are deficient in mismatch repair.

Nevertheless, it remains to be assessed whether the different efficacy observed for 5-FU, according to the tumour mismatch repair status, applies only to this drug and congeners or is a general phenomenon for any therapeutic regimes used as adjuvant chemotherapy. It should in fact be considered that the lack of mismatch repair leads to a high rate of mutations of many different genes, thus possibly increasing the chance of resistance, not only to 5-FU but also to any other drug directed at cancer cells. This reasoning should stimulate chemical–biochemical research to identify compounds that are selectively more effective for cells that are mismatch deficient, an area of research not yet sufficiently explored.

The assessment of biochemical and biological features of the tumour is becoming more and more important in tailoring the optimal therapy for cancer patients, as well demonstrated for endocrine therapy and, more recently, for the drugs directed at specific receptors of growth factors. The assessment of the efficiency of different mechanisms of DNA repair is also becoming more and more important for better use of many anticancer drugs.

For example, the methylation status of the promoter of O6-alkylguanine-DNA-alkyltransferase (AGT) gene – a gene encoding for a protein that removes alkyl groups from the O6 of guanine – appears to be an important factor for the sensitivity of glioblastomas to Temozolomide.[3] The methylation of the AGT gene promoter causes a decreased expression of the repair protein with a consequent reduced rate of repair of the adducts at the O6 guanine and good antitumour activity. It is interesting to note that in preclinical systems the relevance of AGT for Temozolomide sensitivity was already known approximately 20 years before clinical studies were actually published.[4]

The impairment of DNA double strand break repair, related to mutations of BRCA1 or BCRA2, is of great importance in guiding the use of new classes of DNA repair inhibitors, such as PARP inhibitors, and investigating new combinations.

It looks like DNA repair is re-emerging as a very important field, not only in identifying new drugs with different modes of action, but also in how to use already available drugs in a more rational and effective way.[5]

The new study published by Jover et al.[2] is particularly important considering the very high number of patients with intestinal cancer who receive 5FU or it analogues. If other studies confirm these findings, it will be mandatory to assess the status of mismatch repair in colorectal cancer patients before treating the patients as currently oestrogen receptors are determined in breast cancer patients before undertaking anti-oestrogen therapies.

Conflict of interest statement

None declared.

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