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Letter to Editor

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Sister chromatid exchange assay for guiding and improving cancer chemotherapy

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There is a rapid production of micromolecular inhibitors of DNA repair against enzymes which participate in DNA repair mechanisms of DNA damage induced by cancer chemotherapeutics. This development constitutes a successful strategy for identification of antitumor drugs: An important progression was made recently in focusing upon new biological mechanisms and in identifying new mutual cytotoxic effects for revealing antineoplastic drugs in various stages of preclinical and clinical investigations [1,2]. Methylxanthines Benzamide 3-Aminobenzamide which have been tested in cellular cultures are active inhibitors of Poly(ADP-ribose)polymerase (PARP). This chromosomal enzyme catalyzes the synthesis of homopolymeric nucleic acid Poly(ADP-ribose) (PAR). The polymeric is implicated in DNA metabolism especially in the repair process of the damaged DNA. As a consequence of enzyme inhibition appears the cell's inability to repair DNA damage with the result enhancement of DNA damage induced by antineoplastics.

The synergistic action of antineoplastics with PARP inhibitors (PARPi) [2] or with other DNA repair inhibitors like vitamin B1 [3], atypical antipsychotics [4] camptothecin [2] may be proved soon very useful in cancer chemotherapy. And indeed some PARPi have been employed recently in several phase 3 trials concerning those cancers with homologous recombination deficiency [1]. This development constitutes a sound example of preclinical cytogenetic biochemical and oncological studies which directed to the desirable result of effective clinical implementation [2]. However there are great difficulties in predicting long term drug response and cancer behaviour due to biological complexity of carcinogenesis and the multiplicity of mechanisms leading to drug resistance. Future combination therapies will identify more candidates for tailored therapies by PARPi and other promising molecules.

There are findings indicating that by identifying Sister Chromatid Exchanges (SCE) in peripheral lymphocytes of cancer patients after their exposure to antineoplastics in vivo might help to establish on an individual basis the rate metabolism and the DNA damage and/or subsequent repair capacity [2]. In combined in vivo-in vitro experiments lymphocytes from cancer patients who had been given antineoplastics in vivo 3 hours before and then treated with DNA repair inhibitors in vitro were found to have synergistically increased SCE rates and cell division delays [2]. The frequency of SCE and the levels of Proliferation Rate Indices (PRI) in the patients own lymphocytes alone or in combination with DNA repair inhibitors were determined before the cytostatic therapy was started and was used as a control for later comparison in each individual case [2]. Studies investigating a relationship between SCE induction and other expressions of genotoxicity have shown a positive relationship between SCE induction alterations in cell cycle kinetics and reduced cell survival [2]. In several studies a strong correlation between SCE induction PRI depression and established antitumour activity was observed [2].

For the first time it was reported synergistic SCE induction in vivo after treatment with aminophylline in combination with chemotherapeutics in lung cancer patients [2]. It is proposed that the capacity of DNA repair inhibitors to enhance in vitro or in vivo the SCE response of human lymphocytes to antineoplastics taken in vivo could be of value as as an inter-individual test system for increasing the therapeutic ratio of combinations of drugs [2]. This approach has been proposed for guiding and improving cancer chemotherapy on an individual basis. Since genotoxic drug exposure and DNA repair are expected to vary among patients, correlating SCE frequencies with only individual DNA repair capacity may be feasible to predict.

It has been observed a synergism in in vivo SCE induction and in PRI suppression of Ehrlich ascites tumor (EAT) cells after simultaneous treatment with Cyclophosphamide (CP) and Caffeine (Caf). It was also established that CP plus Caf treatment enhances survival of mice inoculated with EAT cells and reduces the volume of ascites tumor in comparison with mice which have been inoculated with CP alone. In this report it is proposed that we may have better therapeutic effects and reduced cytotoxicity by lowering CP dose and by adding in the therapeutic scheme non toxic concentrations of Caf [2]. The same proposal has been made and for other combinations of antineoplastics with DNA repair inhibitors which were identified to suppress Mitotic Indices to reduce PRI and to act synergistically in SCE induction [2]. The observed wide range of SCE for EAT cells after CP treatment indicates drug response for cells derived from neoplasms that are mixtures of sensitive and resistant cells in situ. This wide range narrows however for EAT cells after the combined CP plus Caf treatment [2]. A variety of agents and combinations of drugs can be tested simultaneously on cells to determine which treatment would most effectively induce damage to resistant cells [2].

In many investigations potential antineoplastics and new antineoplastic schemes were tested in search for a possible relationship between genotoxic and cytostatic activity in vitro in normal cells and antineoplastic activity in vivo in cancer cells Ehrlich, P388 and L1210 [2,5]. In these studies it was established that the order of the cytogenetic

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in vitro and in vivo effects of the compounds tested coincides with the order of the antitumour effectiveness they induce [2,5]. Unrepaired DNA damage expressed as SCE in normal cells induced by certain chemicals may indicate inability to repair damage induced by the same chemicals in malignant cells since both cell types have similar DNA repair mechanisms [2]. In these extensive numerous studies [2-5] appears that the hypothesis about a correlation of the effectiveness in SCE induction by potential antitumour agents in normal human cells in vitro and in cancer rodent cells in vivo with the in vivo tumor response to these agents is further substantiated. As a result the SCE assay appears to have an application in prognosis to cancer chemotherapy in assessing interindividual variation in the response to cancer chemotherapy and in quantitating heterogeneity of drug sensitivity among cell subpopulation of a tumor.

References

1. Jenysek D, Kim J, Duijf P, Dray E (2021) Clinical use and mechanisms of resistance for PARP inhibitors in homologous recombination cdeficient cancers. *Transl Oncol* 14: 101012. [Crossref]

2. Mourelatos D (2016) Sister chromatid exchange assay as a predictor of tumor chemoresponse. *Mutat Res Genet Toxicol Environ Mutagen* 803-804: 1-12. [Crossref]

3. Giarma E, Mpampali Z, Lialiaris Th, Mourelatos D (2019) Cytoprotective and genetoxic effects of vitamins K1 and B1 on irinotecan in vitro. *Mutat Res Genet Toxicol Environ Mutagen* 837: 60-64. [Crossref]

4. Katsioulis E, Argyraki M, Ekonomopoulou T, Mourelatos C, Iakovidou-Kritsi Z, et al. (2020) Typical versus atypical antipsychotis: Genotoxicity and cytostaticity testing. *Integr Cancer Sci Therap* 7: 1-6.

5. Mourelatos C, Kareli D, Dafa E, Argyraki M, Koutsourea A, et al. (2017) Cytogenetic effects by newly synthesized antineoplastic steroidal alkylators in cultured human lymphocytes. *Clin Res Trials* 3: 1-4.