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Perspectives of Conjoint Application of Heterocyclic Compounds and Classical Chemotherapeutic Agents

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INTRODUCTION

Finding the new applications of the heterocyclic compounds (isoxazoles and isothiazoles) as biologically active substances, in particular, anti-tumor agents, represents high interest for the specialists not only due to the pharmacophore features of heterocyclic fragments [1-3]. There are effective approaches for the synthesis of various heterocyclic compounds. This ensures their synthetic availability and low prime costs. One of the mechanisms underlying anti-tumor effects of both classes of drugs – heterocyclic compounds and classical chemotherapeutic agents is their ability to provoke cellular senescence in the tumor cells [4]. Interest to isoxazoles and isothiazoles rises up progressively due to the high and variable biological activity, demonstrated by their derivatives [1-4]. Noticeably, reactivity of the heterocyclic compounds correlates with the electron density distribution in the cycle.

Nevertheless, many clinical specialists are reluctant regarding the perspectives of anti-tumor therapies based exclusively on the heterocyclic compounds. Why so? First, in most cases, heterocyclic compounds have lower antitumor activity than classical chemotherapeutic agents do. Second, development of the new cytotoxic agents is an extremely cost-intensive process demanding milliards of dollars [5]. Taking into consideration the above, one can propose a new framework for the application of the heterocyclic compounds. The key idea of the framework is that heterocyclic compounds can possible used as adjuvants for the classical chemotherapy [6-9].

At the current stage, one cannot categorically assert the clinical efficacy of this approach. There are, however, several arguments supporting the idea. All chemotherapeutic agents have side effects. Their cytotoxic and cytostatic activity affects not only cancer, but also healthy tissues [10,11]. Despite all the efforts, these problems have no adequate solution so far. Moreover, apart from the cytotoxic action, chemotherapeutic agents can induce tolerance in some types of tumor cells [12,13]. One of the mechanisms underlying this tolerance is activation of Cyclin-Dependent Kinases (CDK). Fortunately, isothiazole derivatives effectively inhibit CDK8 and its paralog CDK19 [12], suppressing tumor cells proliferation [13-16]. This explains synergism, observed in the experiments with the combinations of heterocyclic compounds and classical chemotherapy. Isothiazoles in combination with chemotherapeutic agents provoked an intensive death of the tumor cells *in vitro* [6,8] and increased the survival rate in the animal tumor models [7,9].

In most cases, classical chemotherapy not only kills the tumor cells, but also stimulates gene expression in the damaged tissues, provoking synthesis of the tumor-supporting factors. It was found that phenotype of these factors results from the activation of CDK-interacting protein p21 (CDKN1A) [15]. Low-molecular compounds inhibiting p21 transcription were identified as selective inhibitors of the CDK8 and CDK19, which are the key

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player in the transcription process [13]. Interestingly, p21 binds CDK8 stimulating its kinase activity. CDK8 inhibitors suppress the paracrine activity of both – tumor cells and normal fibroblasts – promoting the adaptation of the tumor cells to the new conditions after chemotherapy [14]. Thus, CDK8, playing an important role in the processes of tumor epithelial–mesenchymal transition and invasion, represents an attractive target for the new anti-tumor therapies [16]. In general, tumor cells contain various targets, acting on which heterocyclic compounds can suppress the tumor cells proliferation.

CONCLUSION

Therefore, currently, there is a clear understanding of some mechanisms underlying the efficacy of the conjoint action of heterocyclic compounds and classical chemotherapeutic agents. This is further supported by the experimental results demonstrating that addition of the heterocyclic compounds allows decreasing the effective dose of chemotherapeutic agents by one or even two orders of magnitude [6-9,17]. Decrease of the cytostatic dose, in its turn, will reduce the side effects of the therapy [6-9,17] bonus that cannot be overemphasized.

REFERENCES

1. Bouchmaa N, Mrid RB, Boukharsa Y, Bouargalne Y, Nhiri M, et al. (2019) Reactive oxygen species-mediated apoptosis and cytotoxicity of newly synthesized pyridazin-3-ones in P815 (murin mastocytoma) Cell Line. Drug Res (Stuttg).
2. Lucescu L, Ghinet A, Shova S, Magnez R, Thuru X, et al. (2019) Exploring isoxazoles and pyrrolidinones decorated with the 4, 6-dimethoxy-1, 3, 5-triazine unit as human farnesyltransferase inhibitors. Arch Pharm (Weinheim) 352: e1800227.
3. Shin HJ, Hwang KA, Choi KC (2019) Antitumor effect of various phytochemicals on diverse types of thyroid cancers. Nutrients 11: pii: E125.
4. Rasool F, Nayak D, Katoch A, Faheem MM, Yousuf SK, et al. (2017) Regiospecific synthesis of ring A fused withaferin A isoxazoline analogues: Induction of premature senescence by W-2b in proliferating cancer cells. Sci Rep 7: 13749.
5. Hollmann S, Moldaver D, Goyert N, Grima D, Maiese EM (2019) A U.S. cost analysis of triplet regimens for patients with previously treated multiple myeloma. J Manag Care Spec Pharm 25: 449-459.
6. Kulchitsky VA, Potkin VI, Zubenko YS, Chernov AN, Talabaev MV, et al. (2012) Cytotoxic effects of chemotherapeutic drugs and heterocyclic compounds at application on the cells of primary culture of neuroepithelium tumors. Med Chem 8: 22-32.
7. Kulchitsky VA, Alexandrova R, Suziedelis K, Paschkevich SG, Potkin VI (2014) Perspectives of fullerenes, dendrimers and heterocyclic compounds application in tumor treatment. Recent Patents Nanomed 4: 82-89.
8. Potkin VA, Kletskov AV, Petkevich SK, Pashkevich SG, Kazbanov VV, et al. (2015) Synthesis of water soluble isoxazol-3-yl(isothiazol-3-yl) carboxamides and ureas containing amino acid residues – potential anticancer agents. Heterocyclic Lett 1: 11-19.
9. Kulchitsky V, Zamaro A, Alexandrova R, Potkin V, Suziedelis K, et al. (2018) Prospects for improving the effectiveness of chemotherapy in patients with tumors. Biomed J Sci Technol Res 6: 1-3.
10. Wojtukiewicz MZ, Politynska B, Skalij P, Tokajuk P, Wojtukiewicz AM, et al. (2019) It is not just the drugs that matter: The nocebo effect. Cancer Metastasis Rev 38: 315-326.
11. Abd El-Hack ME, Abdelnour S, Alagawany M, Abdo M, Sakr MA, et al. (2019) Microalgae in modern cancer therapy: Current knowledge. Biomed Pharmacother 111: 42-50.
12. Porter DC, Farmaki E, Altilia S, Schools GP, West DK, et al. (2012) Cyclin-dependent kinase 8 mediates chemotherapy-induced tumor-promoting paracrine activities. Proc Natl Acad Sci U S A 109: 13799-13804.
13. Chen M, Liang J, Ji H, Yang Z, Altilia S, et al. (2017) CDK8/19 Mediator kinases potentiate induction of transcription by NFκB. Proc Natl Acad Sci U S A 114: 10208-10213.
14. Ono K, Banno H, Okaniwa M, Hirayama T, Iwamura N, et al. (2017) Design and synthesis of selective CDK8/19 dual inhibitors: Discovery of 4,5-dihydrothieno[3',4':3,4]benzo[1,2-d]isothiazole derivatives. Bioorg Med Chem 25: 2336-2350.
15. Roninson IB, Győrffy B, Mack ZT, Shtil AA, Shtutman MS, et al. (2019) Identifying cancers impacted by CDK8/19. Cells 8: pii: E821.
16. Serrao A, Jenkins LM, Chumanevich AA, Horst B, Liang J, et al. (2018) Mediator kinase CDK8/CDK19 drives YAP1-dependent BMP4-induced EMT in cancer. Oncogene 37: 4792-4808.
17. Kulchitsky V, Zamaro A, Potkin V, Gurinovich T, Koulchitsky S (2018) Prospects of chemotherapy side effects minimization. Cancer Oncol Open Access J 1: 15-16.