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Possibilities of Minimization of Side Effects of Anticancer Chemotherapy

ZV Kaliadzich[1], AS Zamaro[2], SV Goubkin[2], SV Koulchitsky[3], K Suziedelis[4] and VA Kulchitsky[2*]

[1]*NN Alexandrov National Cancer Centre, Belarus*

[*2]*Institute of Physiology, National Academy of Sciences, Belarus*

[3]*Liege University, Liege, Belgium, Europe*

[4]*National Cancer Institute, Vilnius, Lithuania.*

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INTRODUCTION

Anticancer chemotherapy is one of the standard ways of treatment of oncologic patients. Despite the extraordinary high cost of development and study of new anticancer chemotherapy drugs, the synthesis of new chemical antitumor substances continues. Unfortunately, chemotherapy has many side effects, cytostatic and cytotoxic effects on non-tumor cells of living organisms are the main ones. Paradoxically, relatively few topical scientific articles are devoted to this clearly negative property of chemotherapy drugs with respect to non-tumor cells. The search for "cancer chemotherapy side effect minimization" revealed only 5 articles within PubMed on August 20, 2019. This can be possibly explained by the fact that the side effect of cytostatics is not difficult to assume, given the multifactorial mechanisms of their action at the level of DNA, RNA, enzymes, mitochondria, ribosomes, microtubules, spindle, cell membrane, etc. The negative mechanisms of chemotherapy primarily affect the energy activity of living cells, a variety of enzymatic pathways, protein synthesis, mitochondria activity, DNA replication mechanisms, cell division and other natural mechanisms that are the basis of normal life of any living cells. The ideal way out of this situation is to create new chemotherapeutic drugs with no or minimal side effects in relation to non-tumor cells. Pharmaceutical companies are working in this direction, but, as you know, this process is extremely expensive and still has not ended with the creation of a new chemotherapy without side effects. Therefore, it is advisable to look for new methodological solutions to the problem.

There is another intriguing question in solving this problem. Existing recommendations for preclinical and clinical studies include *in vitro* experiments (monolayer of cells, i.e., 2D construction) and 3D observations, that is, *in vivo* experiments in acute or chronic observations. It is important that the pronounced antitumor effect *in vitro* manifests itself *in vivo* differently often during testing of new drugs and is sometimes replaced by the opposite proliferative effect. And even more difficult problem lies in a wide variety of individual patient sensitivity.

The authors decided to focus on the problem of minimization of side effects when chemotherapy is combined with nanoparticles, which are traditionally used for diagnostic purposes, both in experimental and clinical settings. Some researchers are trying to find a kind of replacement for existing drugs, developing combinations of nanoparticles in order to achieve a pronounced antitumor effect [1-3]. For example, the use of nanoparticles in the treatment of melanoma allows increasing stability of standard antitumor drugs, improve permeability of epithelium for chemotherapeutic agents and carry out a peculiar "targeting" of chemotherapy drugs to melanoma cells [1]. Such tactics of new antitumor drugs use is extremely expensive and, unfortunately, still not effective enough. A range of researchers try using nanoparticles as a kind of carriers of chemotherapeutic agents, which allows increasing targeted action of chemotherapeutic agents and reducing their side effects. It was found that induction chemotherapy in combination with chemoradiotherapy significantly improves patients' survival compared to chemoradiotherapy alone in nasopharyngeal carcinoma [4].

In fact, there are solutions that affect the interests of both patients in terms of antitumor efficacy and developers of new drugs. Previous studies at the Brain Center (the Institute of Physiology of the National Academy of Sciences of

Corresponding author: VA Kulchitsky, Institute of Physiology, National Academy of Sciences, Belarus, E-mail: vladi@fizio.bas-net.by

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Belarus) showed that the antitumor activity of classical anti-tumor drugs (cisplatin, methotrexate) was preserved [5] when combined with nanoparticles [5-8] (fullerenes, dendrimers, gold nanoparticles) [5-8].

There is a rational way out of this situation: the method of using a classical chemotherapy in combination with nanoparticles to increase the effectiveness of a combination of substances, which will reduce the dose of a chemotherapeutic drug, but maintain its antitumor effect. Since all chemotherapy drugs have pronounced toxic action (side effects), a reduction in the dosage of chemotherapy drug is the basis for reducing side effects. *In vivo* and *in vitro* experiments were performed in previous studies in the first stages of new technique screening in order to identify those dosages of nanoparticles at which their antitumor results are not manifested. Thus, a new step has been taken to reduce the toxicity of nanoparticles in future drug combinations. In addition, selection from a variety of chemotherapeutic drugs was based on their combination with nanoparticles, which were used in indifferent doses, but in combination with cytostatics allowed achieving antitumor effects *in vivo* and *in vitro* with reduction in dosage of chemotherapeutic agents by 10, 100 and even 1000 times [5-8]. *In vitro* experiments demonstrated antitumor activity of nanoparticles with several chemotherapeutic agents (Cisplatin, Carboplatin, Etoposide, Cytarabine, Methotrexate, Gemcitabine) in relation to C6 glioma [5] and cells of primary brain tumors from the intraoperative material of the Republican Scientific and Practical Centre of Neurosurgery and Neurology of the Ministry of Health of the Republic of Belarus [5-7]. In this case, it is inexpedient to distract the attention of specialists on questions about induction, cytoreductive or another form of chemotherapy, considered in this article. These issues will be important at the stage of technology introduction into clinical practice in the design of clinical protocols.

Antitumor effects seemed paradoxical in severity when nanoparticles were combined (dosages were used at which tumor cell death did not develop) with classical chemotherapeutic agents at the first stages of new technique *in vitro* testing [5]. But namely a combination of nanoparticles and chemotherapeutic agents allowed achieving the death of tumor cells in *in vitro* experiments in those ratios that were equivalent to cell death when using chemotherapeutic drugs in dosages recommended in international community protocols. So, let us pay attention once again that the paradox of the experiment lied in the fact that nanoparticles in dosages that do not have toxic antitumor effects, when combined with chemotherapeutic drugs, can achieve basically total death of tumor cells. Such effect is desirable for an oncologist, but cannot be achieved in reality with sole action of chemotherapeutic agents. However, combination of nanoparticles and chemotherapeutic agents, which allows reducing the doses of cytostatics by tens and hundreds of times preserves targeted antitumor efficacy of chemotherapeutic drugs, comparable to that recommended in international tumor therapy protocols [5-7].

Unfortunately, the mechanism of such increased antitumor efficacy of the combined action of nanoparticles and chemotherapeutic agents is still not clear. It is hypothetically assumed that dendrimers act as peculiar carriers of chemotherapeutic agents and increase due to their three-dimensional structure the interaction density of cytostatics with tumor cells. Such phenomenon is one of the conditions for increase in concentration of antitumor substances in various parts of tumor tissue. Fullerenes can increase permeability of chemotherapeutic agents into tumor cells cytosol [5-8]. Therefore, the likelihood of a more effective antitumor activity of chemotherapy drugs is increased. Such conclusions are hypothetical at this stage of research and open prospects for new projects to clarify the mechanisms of antitumor effects.

So, there is an experimentally identified phenomenon of the ability of nanoparticles in indifferent doses in combination with chemotherapeutic agents to reduce their dosages recommended by international protocols by tens of times. The lower is the dose of chemotherapy drug, the less normal cells and tissues of the whole organism are damaged, the proliferative potential of endogenous stem cells is preserved [9] and, thus, the life of patients with fatal oncological process is prolonged.

There is an important fact of the so-called rebirth of classical chemotherapy drugs [8-10]. We are talking about reduction of side effects of these substances when combined with nanoparticles (it is important to use nanoparticles in indifferent dosages). Such strategy is attractive for pharmacological companies, since previously developed production technologies will allow increasing the effectiveness of previously developed chemotherapeutic drugs considering the new methodology and, thus, increasing the profitability of production [11]. The oncological process is multifactorial. It is necessary to make maximum use of synergistic effect of combination therapy to achieve the maximum therapeutic result in cancer patients [12,13]. Such strategy will make it possible for positively use the features of therapeutic agents to overcome natural heterogeneity of tumors in a particular patient, taking into account his individual characteristics.

CONCLUSION

The problem of radical therapy for cancer patients has not yet been resolved. The lack of a clear idea of the mechanisms of carcinogenesis is one of the reasons for this situation in oncology. The search for new therapies in oncology continues along with the search for an answer to the question of the origins of uncontrolled proliferation of tumor cells. The authors draw readers' attention to the additional resources of chemotherapy that are discovered by

combining classical chemotherapy with nanoparticles. Reduction in dosages of chemotherapy drugs, which is accompanied by weakening of their toxic side effects while maintaining high antitumor activity, is one of the positive consequences of such combinations.

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REFERENCES

1. Chou YP, Lin YK, Chen CH, Fang JY (2017) Recent advances in polymeric nanosystems for treating cutaneous melanoma and its metastasis. Curr Pharm Des 23: 5301-5314.
2. Li J, Chen R, Ji M, Zou SL, Zhu LN (2015) Cisplatin-based chronotherapy for advanced non-small cell lung cancer patients: A randomized controlled study and its pharmacokinetics analysis. Cancer Chemother Pharmacol 76: 651-655.
3. Ang CY, Tan SY, Zhao Y (2014) Recent advances in biocompatible nanocarriers for delivery of chemotherapeutic cargos towards cancer therapy. Org Biomol Chem 12: 4776-4806.
4. Zhang Y, Chen L, Hu GQ, Zhang N, Zhu XD, et al. (2019) Gemcitabine and cisplatin induction chemotherapy in nasopharyngeal carcinoma. NEJM.
5. Shcharbin D, Dzmitruk V, Shakhbazau A, Goncharova N, Seviaryn I, et al. (2011) Fourth generation phosphorus-containing dendrimers: Prospective drug and gene delivery carriers. Pharmaceutics 3: 458-473.
6. Kulchitsky V, Talabaev MV, Chernov AN, Grigoriev DG, Demidchik YE, et al. (2011) Improving the efficiency of chemotherapeutic drugs by the action on neuroepithelial tumors. In: Glioma - Exploring Its Biology and Practical Relevance. Ed. Anirban Ghosh 21: 465-486.
7. 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.
8. 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.
9. Segel M, Neumann B, Hill MFE, Weber IP, Viscomi C, et al. (2019) Niche stiffness underlies the ageing of central nervous system progenitor cells. Nature.
10. Korchagina D, Jaroslawski S, Jadot G, Toumi M (2019) Orphan drugs in oncology. Recent Results Cancer Res 213: 109-142.
11. Conter HJ, Chu QSC (2012) Wise investment? Modeling industry profitability and risk of targeted chemotherapy for incurable solid cancers. J Oncol Pract 8: 69.
12. Pan J, Rostamizadeh K, Filipczak N, Torchilin VP (2019) Polymeric co-delivery systems in cancer treatment: An overview on component drugs' dosage ratio effect. Molecules 24: pii: E1035.
13. Pan J, Mendes LP, Yao M, Filipczak N, Garai S, et al. (2019) Polyamidoamine dendrimers-based nanomedicine for combination therapy with siRNA and chemotherapeutics to overcome multi-drug resistance. Eur J Pharm Biopharm 136:18-28.