World Applied Sciences Journal 12 (8): 1368-1373, 2011
ISSN 1818-4952

Drug Resistance and its Solution in Chemotherapy of Gynecologic Malignant Tumors

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Abstract: Drug resistance is the fundamental reason for tumor recurrence and treatment failure in gynecologic malignant tumors. Drug resistance prevention requires familiarity with physicochemical properties of chemotherapeutic drugs, characteristics of vivo metabolism, correctly chosen chemotherapeutic schemes including multi-drug combination chemotherapy, experimental for doubtful diagnosis and timely assessment to find, treat and prevent serious toxic side effects. Patients should receive sufficient and timely normative chemotherapy as early as possible.

Key words: Chemotherapy · Drug-resistance · Gynecology · Malignant · Ovarian tumor

INTRODUCTION

Chemotherapy, a systemic therapeutic measure, effectively controls the growth, diffusion and metastasis of tumors and cures gynecologic malignant tumors which are highly sensitive after operations. At present, drug resistance to chemotherapy is one of the essential reasons for tumor recurrence and treatment failure. In terms of the mechanism and reasons of its drug resistance, how to prevent, avoid and overcome drug resistance is an important issue in order to improve patients' long-term efficacy and raise their survival rate and will be a long-term task in the research on gynecologic malignant tumors as well [1].

MATERIALS AND METHODS

Index Medicus/ MEDLINE and Science Citation Index were searched for English publications between the years 2000 and 2010 where the studied population included women diagnosed of gynecologic malignant tumors.

Retrospectively, records of 200 patients between the years 1998-2009 were reviewed including patients who did not receive timely post surgery chemotherapy for gynecologic malignant tumors or received non-individualized.

RESULTS AND DISCUSSION

Application of New Chemotherapy Medicine: Conventional chemotherapeutic drugs such as platinum drugs, paclitaxel, doxorubicin and so on can produce new generation of chemotherapeutic drugs through a certain transformation, increasing drugs sensitivity, lowering toxic side effects, which can be applied in treating gynecologic malignant tumors with drug resistance, such as liposome doxorubicin, oxaliplatin, irinotecan and so on. Additionally, phenoxodiol, a small molecular anticarcinogen, can be singly applied to treat hormone refractory prostate cancer and is sensitizing agent of chemotherapy for advanced cervical cancer, vaginal carcinoma and advanced ovarian cancer; NOV-002, a compound based on oxidized GSH, is protective agent of chemotherapy and immunomodulator, which has been approved a combination with chemotherapeutic drugs in Russia to treat ovarian cancer and non-small cell lung cancer [2].

Anti-Angiogenesis Therapy: Inhibiting tumor vessels' formation is one effective way to stop tumor growth. Anti-angiogenesis drug, a chemotherapeutic drug, has many advantages, compared with other ordinary drugs with cell toxicity: First, anti-angiogenesis drug does not depend on tumor types and additionally has nothing to do with the

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mechanism of drug resistance of tumor cells. Secondly, among adults, vessels form only under some specific circumstances, so toxic side effects happen rarely. At present, there are more than 75 kinds of anti-angiogenesis drugs having been under clinical experiment. Most of them are under Phase I and Phase II of clinical experiment. 12 kinds out of them are under Phase III of clinical experiment, such as avastin, vascular enzyme and so on [3].

Targeted Therapy: Input drugs with cell toxicity more specifically to tumor tissue expressing corresponding receptor so as to selectively kill tumor cells; normal tissues without expressing this receptor will be exempt from being infringed to lower toxic side effects from systematical chemotherapy; therapeutic dosage can be raised, moreover, overcome some tumor cells' inherent tolerance for chemotherapeutic drugs. Such as erlotinib, gefitinib and so on, because of their unique antitumor mechanism, no toxic side effects occur in blood system, it is convenient for administration. In cell line of ovarian cancer vitro paclitaxel drug resistance, erlotinib not only has no cross drug resistance but also quite high sensitive degree.

According to the feature of multi-drug resistance in ovarian cancer, after the recurrence of ovarian cancer, change chemotherapeutic drugs and formulate the second line chemotherapeutic scheme, adopting chemotherapeutic scheme without platinum or extending therapeutic interval without platinum to reverse partial acquired drug resistance. But for the patients with acquired drug resistance who have recurrence within six months after stopping chemotherapy, patients with persistent and refractory ovarian cancer who have drug resistance, new chemotherapeutic drugs without cross drug resistance or scheme should be adopted to the best, tumor progression-free period should be extended as long as possible. At present it is reported about therapeutic drugs and scheme as follows: (1) oral etoposide (VP-16): for ovarian cancer with drug resistance, usually adopt 21d oral scheme, on average daily 50mg/m^2, more than 32% remission rate can be achieved. (2) Liposome adriamycin (caelyx): usually take a dosage of 50mg/m^2 per day, three weeks is a course of treatment, single drug can reach 15% remission rate for drug-resistance patients. (3) topotecan: according to the standard scheme, 1.5mg/m^2 per day, 5d non-stop is a course, the total remission rate for platinum drug-resistance patients of ovarian cancer can reach around 15%, successfully delaying tumor progression. (4) gemcitabine (gemzer): usually adopt weekly therapy, administrated together with platinum (on the first day platinum is added), 21d is one course of treatment, on the first and eighth days gemzer 1000mg/m^2, 30~60min input is administered, or on the first, eighth and fifteenth days drugs are administrated, 28d is one course. Together administrated with platinum and paclitaxel in chemotherapy, clinical remission rate can reach 43%~70%. (5) oxaliplatin (L-OHP): can be administrated alone or administrated by combination with other drugs, recommended dosage is 100~130mg/m^2 per day, one administration/ three weeks, when clinically administrated together with cyclophosphamide, administration interval is the same with conventional PC scheme; or always administrated with gemcitabine, remission rate can reach 15%~30%[4].

DISCUSSION

Patients with gynecologic malignant tumors initially have a reaction to chemotherapy. Patients with more than six months' cancer-free plastochron are sensitive to chemotherapy. During the initial chemotherapy period, if the disease progression happens, the best relief is the size of lesion has no change or cancer-free plastochron is less than six months, which is considered as drug resistance to chemotherapy. The drug resistance to chemotherapy of the majority of patients with gynecologic malignant tumors is defined as acquired drug resistance. Nevertheless multi-drug resistance (MDR) of tumor cells is one of the key factors for chemotherapy failure.

Decrease in Concentration of Chemotherapy Medicine in Tumor Cells:

- Related with MDR1 Gene and Amplification and Over Expression of P-gp Glycoprotein in Tumor Cells.

Relevant drugs of chemotherapy include such natural source as anthracycline, vinblastine, epipodophyllotoxin, actinomycin D, paclitaxel and so on and some hydrophobic drugs of chemotherapy. MDR1 gene is the most potent index, which can foresee the drug resistance of tumor patients. Reversal Strategy: for the time being, the research on inhibitor of P-gp glycoprotein has developed into the third generation. The first generation of inhibitor of P-gp glycoprotein includes verapamil, cyclosporine, tamoxifen and some protein antagonist of calcium regulation. *In vitro* experiment, multi-drug

resistance of tumors can be reversed and even completely reversed. While, *in vivo* test, the concentration required in effective reversal of multi-drug resistance vitro cannot be reached due to self dosage limitation toxicity. The second generation of inhibitor of P-gp glycoprotein has been synthesized on the basis of structure reformation of the first generation, mainly including dexverapamil, dexniguldipine, valspodar, biricodar and etc., among those valspodar and biricodar are representative. The third generation of inhibitor of P-gp glycoprotein has made up the disadvantages of the second generation through structure activity and combinatorial chemistry and its representative drugs include tariquidar and XR-9576. A clinical experiment proves that tariquidar and XR-9576 have decreased IC50 value of doxorubicin, paclitaxel and vinorelbine from 2.57, 27.4 and 15.5mmol/L to 1.67, 20.6 and 9.5mmol/L [5,6].

- Multi-drug Resistance Protein (MRP), Lung Resistance Protein (LRP) and Breast Cancer Resistance Protein (BCRP) are a group of protein related with multi-drug resistance of tumor cells [7].

Reversal Strategy: at present we haven't found any low-toxicity and effective MRP reversal agent. Researchers found that verapamil can reverse not only MDR1 but also MRP; cyclosporine A can reverse MDR1 but not MRP; whether paclitaxel can reverse MRP or not, which still needs a further study. One pyridine analogue PAK-104P and anti-LRP antibody can increase adriamycin accumulation in cell nucleus and inhibit adriamycin flowing from cell nucleus to cytoplasm. Therefore, it is considered that PAK-104P can be applied in reversing MDR mediated by LRP [8].

Increase in Metabolic Detoxification of Chemotherapy Medicine in Cells: Increase of level and activity of glutathione (GSH) and glutathione S transferase (GST) in cells is the possible mechanism for drug resistance of tumor cells. Content increase of GSH and activity enhancement of GST on the one hand result in increasing drug polarity, losing toxicity, on the other hand are more easily transported out of cells after they are coupled with drug, hence, cells show MDR phenotype. Reversal Strategy: buthioninesulfox imine (BSO) is one synthetic amino acid analogue and inhibitor of GSH synthase, by inhibiting from synthesizing to reverse tumor drug-resistance, which is under the second phase clinical experiment abroad. The drugs with similar effect are as follows: nitroimidazoles, paracetamol, sodium selenate and selenocystein. The researches proves that combined medication leads to a better reversal effect [9].

Increase in DNA Repair in Cells: After tumor cells have formed drug resistance, DNA repair will be increased in the cells so that impaired DNA by drugs will be corrected with the aim to decrease cell toxicity and continue cell division. Reversal Strategy: at present inhibitors of DNA polymerase applied in the first phase clinical experiment include aphidicolin, Lu103793 and so on, which inhibit DNA repair by inhibiting DNA polymerase to reverse drug resistance. Phase I clinical experiment indicates that aphidicolin only has local toxicity effect and its maximum tolerant dosage can reach 4500mg/m^2. This kind of drug has a good clinical tolerance [10].

Decrease in Topoisomerase Quantity Activity: Topoisomerase is the enzyme needed for DNA replication and transcription. It has two subtypes. One of its main function is to adjust and control DNA supercoiled state and knotting or unknotting DNA ring connecting body state in order to indirectly influence metabolism process of nucleic acid in cells. The other function is to directly join in the cell process of breaking and reuniting DNA molecular chain and the process of DNA recombination, repair, transcription and replication. The quantity of enzyme will be changed. Reversal Strategy: type I inhibitor contains camptothecin, actinomycin D and so on. Type II inhibitor contains some acridine, epipodophyllotoxin, anthracycline and anthraquinones.

Increase in Protein Kinase C (PKC) Activity: PKC is a group of Ca^{2+}/isoenzyme phospholipid dependent. Actual researches suggest that PKC can make P-gp glycoprotein or MRP phosphorylate and get activity, which is one of the important mechanisms of multi-drug resistance. Reversal Strategy: Present researches show that inhibiting PKC activity can antagonize MDR. At present the inhibitors of PKC include NA2382 (derivatives of staurosporine), CGP41251, K2252a, CalphostinC, H27 and so on.

p53 Gene Mutation and So On: For the time being many researchers suggest that p53 gene plays a very important role in platinum-based drug resistance in ovarian cancer. Platinum drugs can result in DNA damage. When the damage occurs, the defunctionalization of p53 is one of the main reasons resulting in tumor drug resistance.

Reversal Strategy: at present p53 has become the main orientation of gene therapy research. Transfect wide type p53 to tumor cell strains without p53 expression, producing tumor inhibition and molecule change, synchronizing with stagnation and apoptosis of cell period. Wide type p53 gene combines with taxol, cisplatin, adriamycin and other drugs to more effectively inhibit the growth of tumor cells [11, 12].

Factors for Drug Resistance to Chemotherapy: There are many factors resulting in drug resistance of chemotherapy of gynecologic malignant tumors. Possibly related with the following aspects: (1) the dosage of chemotherapy drugs and therapeutic course are not enough, resulting in tumor cells not being completely eliminated but temporarily latent, which will bring out future drug resistance and recurrence. (2) the choice of chemotherapy scheme is not reasonable, without considering individual case to choose sensitive chemotherapy drugs, tumor cells cannot be specifically and effectively controlled, inducing drug resistance. (3) doctors' prescription for chemotherapy is not normative, delaying the chemotherapy opportunity due to not receiving timely chemotherapy as soon as possible after the operation; in terms of patients' cooperation, many patients stop the therapy without authorization due to physique, economic problems and other reasons; many patients would not like to suffer from the side effect resulting from chemotherapy and the side effect cannot be corrected effectively, so the patients do not receive the chemotherapy on time any more or intermission is not regular, finally drug resistance will occur. (4) clinical doctors are not thoroughly familiar with the functional mechanism and features of all chemotherapy drugs, so they do not make an individual therapy scheme from the perspective of evidence-based medicine and cannot find and solve the specific problems in time during chemotherapy process. Thousands of patients, the same prescription results in drug resistance [13].

CONCLUSION

Application of the below mentioned treatments may prevent drug resistance to chemotherapy.

Selection of Reasonable Chemotherapy Scheme: As far as malignant tumors of ovary are concerned, the chemotherapy schemes often adopted are PC, PVB, CAP, CBP, TP, TTP, VBP and so on, in order to lower occurrence rate of drug resistance, being fully familiar with physicochemical properties of chemotherapeutic drugs, characteristics of vivo metabolism and anti-tumor mechanism is required, so that chemotherapeutic drugs can be rationally applied. On the basis of acquiring pathological diagnosis of gynecologic malignant tumors, surgical-pathologic staging or clinical staging of gynecologic malignant tumors will be confirmed, by referring to tumor markers and imaging data, putting forward specific chemotherapeutic indication and purpose, pertinently and correctly choose chemotherapeutic schemes. If the diagnosis is doubtful, any experimental chemotherapy should be carried out on patients, resulting in delaying disease and tumors' drug resistance for chemotherapy and finally influencing chemotherapeutic effect. A timely assessment on patients should be done as soon as when chemotherapy has been finished, including efficacy, toxic side effects and so on. Finding, treating and preventing serious toxic side effects in time is the basic guarantee for completing the whole chemotherapy scheme. Based on the assessment, adjust chemotherapy dosage and scheme in time in order to treat cancer at its best and lower influence on patients from its toxic side effects [14-16].

Receive Sufficient and Timely Normative Chemotherapy as Early as Possible: According to patients' specific state after operation, chemotherapy should be carried out as early as possible. After researches Buller and other experts put forward that three years' survival rate of patients will be influenced if there is more than three weeks' interval between chemotherapy and operation. Taxol, topetican and other drugs should be administrated once every three weeks, other drugs once every three or four weeks, generally three to six courses of treatment are best. Course of treatment should be determined on the basis of the length of increment cycle of tumor cells. Generally it is advocated one course of treatment extends continuous administration for more than two increment cycles of tumor cells or more than two tumor multiplication time. Thus, if some tumor cells are not killed in the first cycle, they can be killed in the second and third cycles. The length of intervals between courses of treatment is the best when drugs' toxicity function almost disappears, normal function of organism almost recovers, killed tumor cells have not been repaired yet. While consolidating every course of chemotherapy, tumor markers (CA125, CA199, AFP, HCG and so on) and imaging (ultrasonic, CT, MRI and so on) should be used to assess efficacy, avoiding blind use[17].

Multi-Drug Chemotherapy: Different tumor cells have different drug resistance mechanism to the same drug and the same cell produces multi-drug resistance mechanism to the same drug. Hence, multi-drug combination chemotherapy can avoid drug resistance from single drug as much as possible. Nevertheless, when combining different drugs, the following aspects should be considered: toxic side effects from different drugs, order of medication, way of medication, dosage, length of course of treatment, interval and so on. It should be paid more attention that it is not more different drugs used, better efficacy can achieve, or it is not accumulation of many kinds of drugs, either. Interaction among different drugs should be noticed and avoid abuse by all means. At present, in China clinically generally adopt the first line chemotherapeutic scheme for ovarian cancer, mainly including carboplatin plus cyclophosphamide, carboplatin plus cyclophosphamide plus adriamycin and taxol or carboplatin and so on; chemotherapeutic scheme for nourishing cell tumor includes EMA/EP or EMA/co and so on; chemotherapy for cervical cancer generally adopts cisplatin combined with 5-FU; chemotherapy for endometrial carcinoma generally adopts PA and PAC schemes [18].

Individual Chemotherapy: Chemotherapy for gynecologic malignant tumors will develop in pursuit of normalization, individualization, humanization and high efficiency and low toxicity. Lowering toxic side effects in chemotherapy, sustaining tissue organs' functions and raising patients' survival quality are the treatment tendency of gynecologic malignant tumors. Because of possible congenital drug resistance of tumor cells or the difference of sensitive degree to chemotherapeutic drugs, or because perhaps the same cell produces multi-drug resistance mechanism to the same drug and other factors, at present test technology vitro antitumor drug sensitivity has been improved and coincidence rate of results of vivo and vitro drug sensitivity has been raised, it is advocated that chemotherapy should be guided in the hospital with good facilities according to test result of drug sensitivity, individualizing chemotherapy. Thus, avoid blindness of chemotherapy, raise efficacy and prevent drug resistance. For the patients receiving the first chemotherapy, fully assess their disease, confirm clinical phases and learn their prognosis in order to formulate suitable schemes [19-20].

In a word, drug resistance in chemotherapy is one of the most major factors for chemotherapy failure of gynecologic malignant tumors. Although the research on drug resistance mechanism has developed greatly till now, certain mechanism is not yet clear. A further exploration is still needed for research on drug resistance and its therapy. Therefore, from the perspective of evidence-based medicine, there is a great significance for extending patients' survival time and raising their quality of life by offering them with reasonable and suitable therapeutic schemes.

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