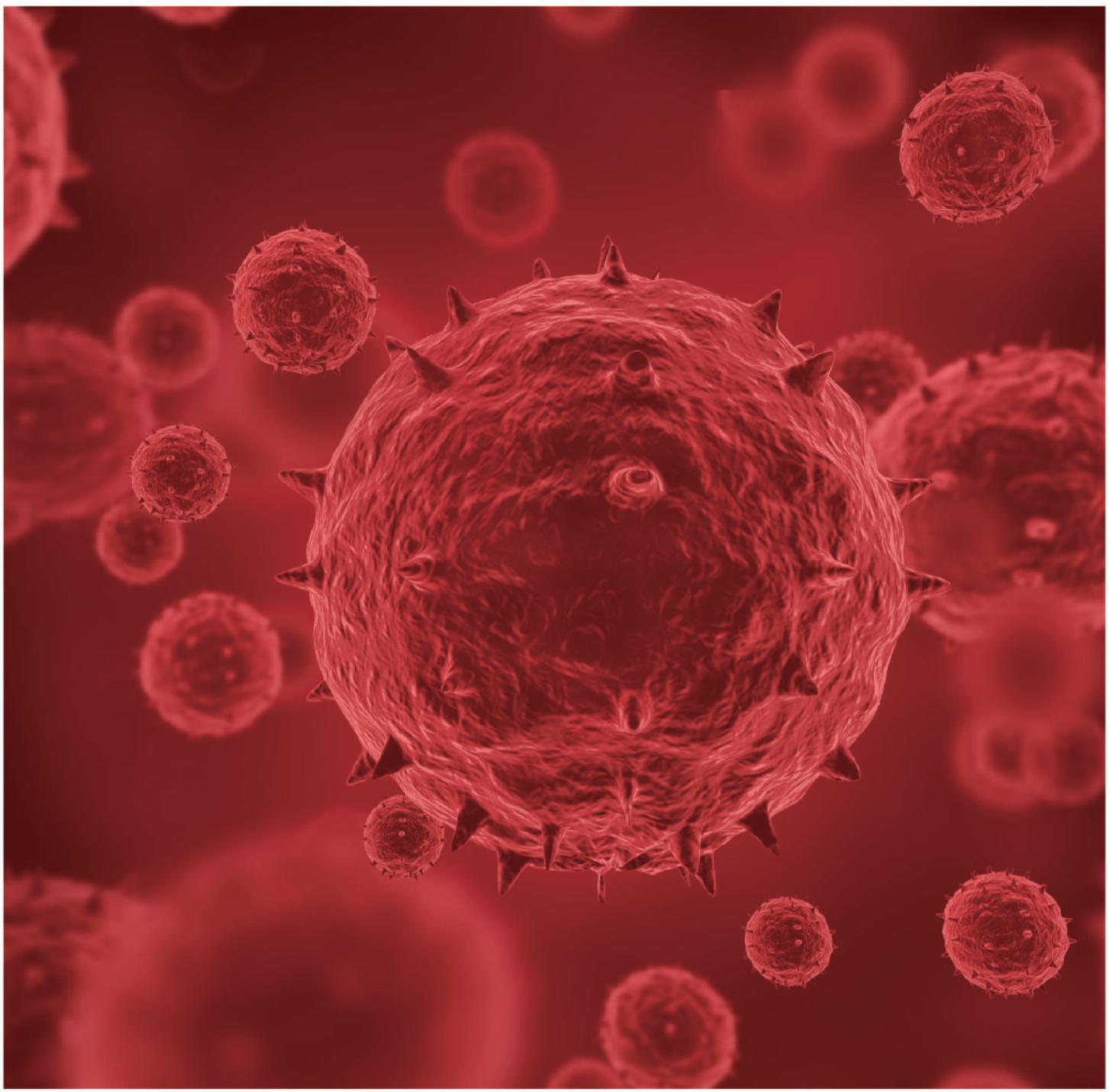
Journal of Oncology Research

Volume 1 | Issue 1 | 2019 April | ISSN 2630-5267 (Online)



BILINGUAL PUBLISHING CO.
Pioneer of Global Academics Since 1984

Volume 1 Issue 1 • April 2019 • ISSN 2630-5267 (Online)

Journal of Oncology Research

BILINGUAL PUBLISHING CO.
Pioneer of Global Academics Since 1984

BILINGUAL PUBLISHING CO.
Pioneer of Global Academics Since 1984

Volume 1 | Issue 1 | April 2019 | Page 1-15
Journal of Oncology Research

Contents

Editorial

Article

Review

BILINGUAL PUBLISHING CO.
Pioneer of Global Academics Since 1984

Journal of Oncology Research
https://ojs.bilpublishing.com/index.php/jor

EDITORIAL

A Foreword from the Editor-in-Chief

Hongwei Chen*

The University of Michigan, United States

ARTICLE INFO

Article history
Received: 14 March 2019
Accepted: 14 March 2019
Published Online: 30 April 2019

Cancer is a devastating disease that suffered so many lives and families throughout of the world, and is becoming an increasing burden to our society. Thanks to the advances in both basic cancer biology and clinical diagnostic/therapeutic treatments, cancer patients' mortality has been significantly decreased in the past decades. Specifically, recent breakthrough in cancer immunology and immunotherapy has shed a bright light for cancer patients to guide them to fight the cancer via harnessing their own immune system, as some patients even with advanced diseases showed long-term remission and durable responses after immunotherapy. Although this new cancer treatment can only benefit a subset of cancer patients, it clearly suggests to us that patient's immune cells have the capability to fight against cancer. It is just a matter of how to use them. As a peer-reviewed open journal, the Journal of Oncology Research is dedicated to publish most cutting edge research with a focus on how cancer invades our immune system and how to develop effective strategies to reverse this invasion. Journal of Oncology Research aims to discover innovative methods, theories and studies in Oncology by publishing original articles, case studies and comprehensive reviews. We hope that Journal of Oncology Research will become an important platform for our scientists to share their exciting results and for our readers to seek fertile and reliable source of information. We will look for research in the following topics, but not limited:

1. Cancer Immunology and Immunotherapy

This topic will cover new basic molecular and cellular mechanisms of interactions between tumor cells and immune system; new therapeutic combinations to boost cancer immunotherapy; and new prognostic indicators.

2. Tumor-derived Exosomes

This topic will cover new findings in understanding how tumor-derived exosomes interact with immune system, tumor immunity, and tumor-associated fibroblasts.

3. Metastasis

This topic will include new findings in investigating novel mechanisms of cancer metastasis including how tumor

**Corresponding Author:*
Hongwei Chen,
The University of Michigan, United States;
Email: hongweic@umich.edu

 DOI: https://doi.org/10.30564/jor.v1i1.634

cells invade primary tissues, exit from circulation into distant organs, and promote niche formation in metastatic organs.

4. Microbiome and Cancer

This topic will cover the new investigations in understanding the role of microbiota in cancer progression and therapeutic outcomes.

5. Cancer Nanotechnology

This topic will include new findings in using nanotechnology for early diagnosis, developing novel nanomedicines for targeting and reprogramming suppressive immune cells, and generating immunogenic cell death in combination with cancer immunotherapy.

6. Tumor Markers and Cancer Early Diagnosis

This topic will cover the identification of novel markers from liquid biopsy including blood-based assessment of tumor-derived and non-tumor derived exosomes to identify a molecular signature that can inform the disease status of cancer.

DOI: https://doi.org/10.30564/jor.v1i1.634

BILINGUAL PUBLISHING CO.
Pioneer of Global Academics Since 1984

Journal of Oncology Research
https://ojs.bilpublishing.com/index.php/jor

ARTICLE

Measurement of AhR Ligands in the Tissues of Colon Cancer Patients with XRE Luciferase Reporter

Bystriakova Margarita Koshkin Sergei Tolkunova Elena*

Institute of Cytology of the Russian Academy of Science, St-Petersburg 194064, Russia

ARTICLE INFO

Article history
Received: 24 Junaury 2019
Accepted: 14 March 2019
Published Online: 30 April 2019

Keywords:
Aryl hydrocarbon receptor
Colon cancer
HEK293T-AhR-luc
Polycyclic aromatic hydrocarbon
XRE luciferase reporter bioassay

ABSTRACT

The Aryl hydrocarbon receptor (AhR) ligands exhibiting modulating activity represents a new class of anticancer agents that can be directed towards several tumors. We have examined AhR expression in human colon cancer and adjacent non-tumor tissue. AhR expression level was about 2-7 times higher in tumor tissue samples than in the adjacent non-tumor samples (in 82% of all the samples). We were unable to find any increase of ABCG2 expression on the level of the transcription, while the expression of MDR2 was increased in half of the tumors compared to the levels of expression in normal adjacent tissue. We have used FICZ as a potent high affinity ligand of the AhR to calibrate the reporter cell line HEK293T-AhR-luc as a potent high affinity ligand of the AhR. The concentration of xenobiotic response element (XRE) ligands is higher, than in the blood of healthy people in 86% of the patients. The proposed test system will allow the use of the AhR ligand level as an additional diagnostic marker in the treatment of colon cancer.

1. Introduction

The presence of polycyclic aromatic hydrocarbons (PAHs) in the environment is a source of concern for specialists in the field of organic chemistry, biochemists, environmental chemists and geochemists. Many PAHs are potent chemical carcinogens [1]. The deterioration of the environmental situation is associated with the increase in cancer incidence, including colorectal cancer. There were approximately 1.4 million new cases of colorectal cancer in 2012, making it the third and second most common cancer globally among men and women, respectively [2].

AhR is an environmental response gene that mediates cellular responses to a variety of xenobiotic compounds that frequently function as AhR ligands. The protein encoded by AhR is a ligand-activated helix-loop-helix transcription factor involved in the regulation of biological responses to PAHs. The AhR that is present in the non-active state is cytosolic. Before ligand binding, AhR is sequestered in the cytoplasm; upon ligand binding, this protein moves to the nucleus and stimulates transcription of target genes after binding to specific DNA sequence elements known as the xenobiotic response elements (XREs). XREs are present in the regulatory region of target genes including xenobiotic-metabolizing enzymes (XMEs) such as members of cytochrome P450 family (CYP1A1, CYP1A2, CYP2B1 and UGT1A6) [3].

Immunostaining of normal intestinal tissue sections

**Corresponding Author:*
Tolkunova Elena,
Institute of Cytology of the Russian Academy of Science, 4 Tikhoretsky avenue, St-Petersburg, 194064, Russia;
E-mail: entolk62@mail.ru

 DOI: https://doi.org/10.30564/jor.v1i1.410

allows the localization of AhR in the stroma that contains immune cells and lymphoid follicles, whereas in the tumor tissue immunostaining was detected in both stromal and tumor cells. Given that, it can be seen that AhR expression is increased in tumor tissues. Enterocytes of the small intestine have a great ability to detoxify PAH, so that the epithelium of the small intestine is the first barrier to the absorption of PAH. Barrier function is provided by XME and efflux carriers that transport metabolites from the cell. ATP-binding cassette subfamily G member 2 (ABCG2) and P-glycoprotein (ABCB1/MDR2) is known for mediating the efflux of conjugated metabolites of xenobiotics [4-6]. ABCG2 is a constitutively expressed ATP-binding cassette (ABC) transporter that protects many tissues against xenobiotic molecules.

In various cancers ABCG2 transporters are known to produce multidrug resistance (MDR), thereby limiting the clinical response to chemotherapy. They show activity that changes the pharmacokinetics of the drugs used and diminishes the effectiveness of their delivery to tumor cells, causing the formation of multidrug resistance. ABCG2 was also identified as a direct target of AhR [7]. AhR abundantly expressed in many different types of cancer. Thus, AhR pathway on one hand assists in the eradication of PAHs, but, on the other hand, the side effect of its activation is a certain decline of treatment efficiency via the chemotherapeutic agent's efflux.

In recent years, the interest of human AHR research has shifted to the study of the physiological functions of AHR and immunity control [8-10]. Along with its involvement in chemical protection, researchers are most interested in its involvement in providing stem cell homeostasis, as well as in modulating the immune system [11].

The identification of tumorigenic cancer stem cells (CSCs) in colorectal cancer and the mechanism contributing to the formation of their qualities and the maintenance of homeostasis requires additional study and remains unidentified.

Significantly increasing the effectiveness of spheroid formation, resistance to chemotherapy and the ability to form tumor xenografts of choriocarcinoma cells after activation of AhR by TCDD has been reported recently. Expression of ABCG2 is also related to tumorigenic CSC in several cancers. The possible role of AhR in CSC quality maintenance is highly interesting to the application of AhR as a marker of CSC and can be used for creating a target drug.

Based on the studies in recent decades, researchers have come to understand the causal role of FCs in several human diseases. The role of AhR as a diagnostic marker and a possible therapeutic target in the treatment of these pathologies is suggested [12].

There are reporter constructions that allow to estimate the activity of the main signaling pathways under the control of the responsive elements to various nuclear receptors by the level of the luciferase expression. Although technically not a member of the Nuclear Receptor superfamily, the AhR shares many of the same attributes. To study the changes in AhR activity we have decided to use XRE luciferase reporter. Our reporter construct is similar to the plasmid from the well-known chemically activated luciferase expression (CALUX) system [13] that has been used for the rapid and inexpensive detection and relative quantitation of dioxin-like chemicals in a wide variety of sample matrices. Although the Caco-2 adenocarcinoma cell line is traditionally used as a model to study the intestinal epithelium, we have decided to use HEK293 cells to make a xenobiotic responsive cell line. The goal of our study was to create a reporter cell line, which will make it possible to estimate xenobiotic concentration in a serum of colorectal cancer patients and in tumor tissue. HEK293 cell line was used for transfection with the reporter construct, which contained the luciferase gene under control of a XRE repeated 6 times and a minimal promotor. The level of Luc expression, measured in the relative units, reflects the concentration of PAHs in the culture media of reporter cells line. To calibrate the reporter cell line we had used FICZ as a potent high affinity ligand of the AhR.

2. Materials and Methods

2.1 Cell Culture

Experiments were done with HEK293T cell line and reporter cell line HEK293T-AhR-luc. The cells were maintained in a DMEM medium (Biolot) with 10% bovine embryonic serum (Gibco), penicillin and streptomycin (Biolot). The cells that have reached the monolayer were subcultured in the ratio of 1:3.

2.2 Tumor and Adjacent Mucosa Samples

Colon adenocarcinoma, adjacent normal tissue and blood serum from 11 patients were used in experiments, these patients were ranked according to the severity and extent of the oncological process, according to the clinico-morphological (TNM) classification (Table 1). Also blood serum from healthy people was used.

DOI: https://doi.org/10.30564/jor.v1i1.410

Table 1. Clinico-pathological characteristics of patients

Patient	Sex	Age	TNM*	Tumor localization
P1	F	67	$pT_{is}N_0M_0G_1$	Transversum colon
P2	F	66	$pT_4N_0M_0G_2$	Transversum colon
P3	F	84	$pT_4N_0M_0G_2$	Transversum colon
P4	M	66	$pT_3N_0M_0G_1$	Transversum colon
P5	M	70	$pT_3N_0M_0G_2$	Transversum colon
P6	F	68	$pT_3N_0M_0G_2$	Cecum
			$pT_3N_1M_0G_2$	Transversum colon
P7	M	63	$pT_3N_1M_0G_2$	Cecum
P8	M	66	$pT_3N_1M_0G_3$	Transversum colon
P9	F	72	$pT_3N_1M_0G_3$	Transversum colon
P10	M	49	$pT_3N_1M_1G_2$ (hepar)	Transversum colon
P11	F	56	$pT_3N_1M_1G_2$ (hepar)	Transversum colon

Note: Main clinico-pathological information of patients. The position in the table was determined based on the clinical prognosis coming from the pTNM classification and additional prognostic markers (level of tumor differentiation, tumor grow rate). F- female, M- male. pTNM - Classification system of the anatomical extent of cancer. p - stage given by histopathologic examination of surgical sample. T - size of primary tumor, N - degree of spread to regional lymph nodes. M – present of distant metastasis and site.

2.3 RNA Isolation, Synthesis of cDNA and qPCR

Total RNA was isolated from cultured cells and tissue samples (with preliminary homogenization) using the RNeasy Mini Kit (Qiagen). cDNA was generated from 1 μg of total RNA per sample using the RT M-MuLV–RH kit (Biolabmix, Russia). qPCR was performed by using the CFX96 Touch Real-Time PCR Detection System (Bio-Rad) and the HS-qPCR SYBR Blue kit (Biolabmix, Russia). GAPDH and B2M genes were used to normalize gene expression. The results are represented as a fold induction using the ΔΔCt method.

2.4 Cloning of XRE and Map of the Reporter Plasmid

The plasmid vector pGL4.27(luc2P/minP/Hygro) was used for XRE cloning. The vector contains a multiple cloning region for insertion of a response element of interest upstream of a minimal promoter and the luc2P gene. The vector contains an ampicillin resistance gene to allow the selection in E. coli and a mammalian selectable marker for hygromycin resistance. KpnI and HindIII sites of the polylinker region were used for restriction and ligation during the preparation of XRE vector under a minimal promoter. The thrice repeated 21 bp XRE was used as an insert. Synthetic oligonucleotides has KpnI and HindIII sites on the ends and after annealing were ready for ligation into the restricted vector. The oligonucleotides sequences are presented below:

F-XRE/KpnI-HindIII (65 bp)

ctg agt tct cac gct agc aga ttg agt tct cac gct agc aga ttg agt tct cac gct agc aga ta

R - XRE/HindIII-KpnI (73 bp)

agc tta tct gct agc gtg aga act caa tct gct agc gtg aga act caa tct gct agc gtg aga act cag gta c

2.5 Reporter Cell line Creation

After the transfection of a plasmid reporter into HEK293T cells with Lipofectamit 2000, clones with integrated construct were selected into the culture media, containing 100 mkg/ml Hygromycin B. Several clones were selected and their response to AhR ligand inducible activation of luciferase expression was checked out. One clone was chosen and used in the presented study as HEK293T-AhR-luc cell line.

To calibrate the reporter cell line we have used FICZ (Merck) as a potent high affinity ligand of the AhR. We used ligand solution in concentration from 100nM to 0.032 nM, because this reporter line was created for working in the range of nearly physiological concentration of PAHs. Luciferase assay was performed by using the Luciferase Assay Systems (Promega). Cell viability was determined with MTT assay after 24 h.

We have determined the expression level of AhR and its surrogate target CYP1A in a reporter cell line in response to the treatment of FICZ. 7. FORMATTING Please, make the figures bigger. Our studies clearly show an mRNA increase for CYP1A in response to the FICZ (0.8 nM) treatment of the reporter line cells.

2.6 Luc-assay

Increased luciferase activity was used to estimate the AhR activation, induced by the components in a culture medium. $1.5x10^4$ cells per well were seeded in a 96-well tissue culture plate in a standard growth medium, 24 hours prior to the test. On the day of the experiment the media was replaced with a fresh growth medium containing 10% heat inactivated patient's blood serum or lysate of patient's tissues. For the preparation of colon adenocarcinoma and adjacent normal tissue

DOI: https://doi.org/10.30564/jor.v1i1.410

lysates 25 mg of each samples were taken and placed in 500 mkl of buffer solution (20 mM Tris pH 7.6; 100 mM MaCl; 5 mM MgCl2; 1 mM EDTA). Then the samples were disrupted and homogenized with the pestle, underwent ultrasound treatment (3 times, 15 sec each impulse in 80% of maximal intensity) and centrifuged for 3 min at maximum speed. The exposure within luciferase assay buffer and substrate was performed by using the protocol for Luciferase Assay Systems (Promega). The cytotoxicity of the compounds screened against the HEK293T-AhR-luc cell line was tested in parallel by measuring the cell viability using MTT-assay. Luminescence intensity of the reaction is quantified using a luminometer, and is reported in terms of Relative Light Units (RLU's) per 100 000 cells. Viability of cells was measured by a colorimetric method using MTTassay. Optical density was measured at a wavelength of 570 nm against a solution of MTT with DMSO on a Multiskan EX spectrophotometer (Thermo Electron, USA). The amount of unsoluble formazan correlates with the number of viable cells in the population.

2.7 Statistics

RNA level and cell viability were evaluated after three identical tests. Statistical difference was calculated in the analysis of variance using Statistica 6.0. $p<0.05$, which was considered to be statistically significant. Mixed-model analysis of variance (ANOVA) or the Student's t test was used to analyze data from the luciferase reporter assays, and P values less than 0.05 were considered as statistically significant.

3. Results

3.1 AhR Expression in Human Colon Cancer

We examined AhR expression in human colon cancer and adjacent non-tumor tissue (figure. 1A). RT-PCR analysis has revealed that the AhR expression level was about 2-7 times higher in tumor tissue samples than in adjacent non-tumor samples (in 9 from 11 samples). For one of patient we have registered a couple hundred-fold of an increase in the level of expression of AhR by qPCR. We have observed the increased AhR expression in tumor cells, however the level of expression was not connected with the stage of the disease.

The results of a comparative analysis of the level of AhR mRNA in groups of patients suffering from different types of cancer were published. The data shows that in the tumor tissue of patients with cancer of the thyroid gland, pancreas, stomach or colon, the mRNA content in the tumor tissue is higher compared to non-tumor tissue. However, as noted by Safe et al. (2013), AhR mRNA levels were not predictive for patient survival [14].

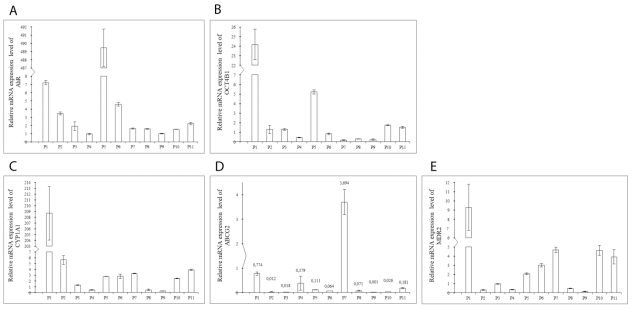


Figure. 1. mRNA expression in patient tissues.

P1-11 - patients with colorectal cancer. From the left to the right, patients are represented by the increased stage of disease according to the classification of TNM staging system. For each patient mRNA level in normal tissue was taken as 1. mRNA expression level is shown in the tumor tissue relative to normal tissue. Height of column above 1 indicates overexpression, below — of its supression. (A) Relative level of AhR mRNA. (B) OCT4B1 mRNA. (C) CYP1A1 mRNA. (D) ABCG2 mRNA. (E) MDR2 mRNA.

We have compared the levels of excess expression of AhR levels in tumor tissue compared to normal tissue with expression levels of OCT4B1, a potential marker of colon cancer stem cells (figure 1B). We have found that in the samples expressing OCT4B1 at an elevated level compared to the adjacent normal tissue, the level of expression of AhR was also increased. We assume that there is a link between the expression level of AhR and the enrichment of the tumor population with stem-like cells potential.

3.2 Expression of CYP1A1 and ABC Family Members in Human Colon Cancer

The biotransformation of potentially toxic chemicals occurs in two distinct phases, Phase I and Phase II, and involves several enzyme systems, the most important being the P450 cytochromes. We have compared the levels of expression of CYP1A1 in tumor samples and adjacent tissues and registered a 2-5-fold increase in 8 samples out of 12 (figure 1C). To eliminate toxins, the body has developed several transporter systems, such as the P-glycoprotein, which prevents the absorption of chemicals through the gastrointestinal tract by facilitating their efflux from the enterocytes into the intestinal lumen [15]. We were unable to find any increase of ABCG2 (figure 1D) expression on the level of tran-

DOI: https://doi.org/10.30564/jor.v1i1.410

scription, while expression of MDR2 (figure 1E) was increased in half of the tumors compared to the levels of expression in normal adjacent tissue. No dependencies of the expression levels of the efflux transporters of the tumor malignancy stage were found.

3.3 Calibration Curve for Reporter Cell Line

To calibrate the reporter cell line we have used FICZ as a potent high affinity ligand of the aryl hydrocarbon receptor (AhR). A descriptive statistics analysis of HEK293T-AhR-luc calibration curve was performed using Excel (Microsoft). In this range of concentrations calibration curve can be described by the following equation y=12.99∗x0.19, where y (RLU's) is the luciferase activity at ligand, (FICZ) is the concentration d (nM) (figure 2A). The coefficient of determination R=0.19 so the model can be considered quite good [16]. A calibration curve allows to determine the concentration of PAH in the tissues of the given patients, converts the Relative Light Units (RLU's) to the concentration of PAH (nM). We consider the change in level of luciferase expression in response to the binding of the PAHs mixture in the sample to be equivalent to the effect of the FICZ. Luciferase activity was correlated to the number of viable cells determined by the MTT method.

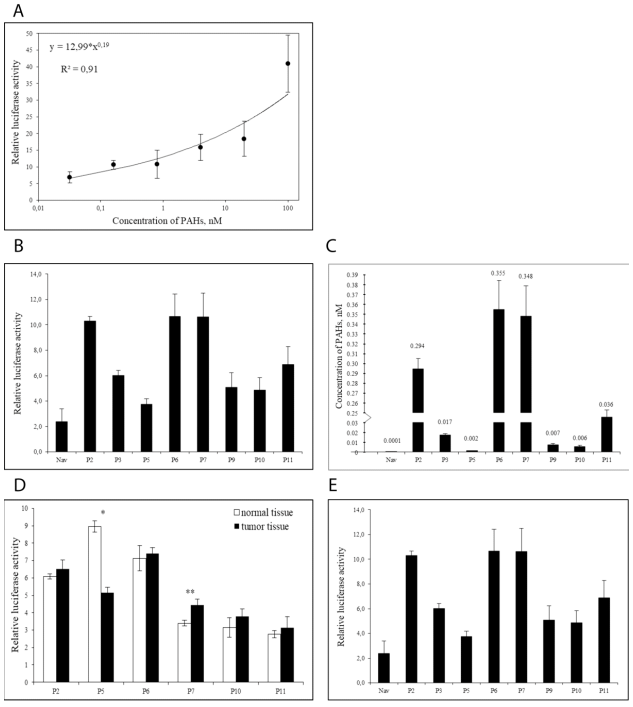


Figure 2. Measurement of AhR ligands (PAHs) concentration.

Note: (A) Calibration curve for reporter cell line HEK293T-AhR-luc. P2-10 - patients with colorectal cancer. Nav (average norm) – average for the blood of 6 healthy people. (B) Concentration of PAHs in blood of patients in RLUs. (C) Concentration of PAHs in blood of patients in nM. (D) Concentration of PAHs in a surgical sample of cancerous and normal tissue in RLUs. (E) Concentration of PAHs in a surgical sample of cancerous and normal tissue in nM. n=3, $p<0.05$.

3.4 The Concentration of XRE Ligands in the Blood of Patients with Colon Cancer

It is known that the defeat of the human body by xenobiotics most often and most effectively occurs through food chains (up to 96% of the PAH enters the human body with food). To answer the question whether the presence of colon cancer correlates with the content of AhR ligands in the blood serum, we have compared the effect of the blood serum of sick and healthy people on the level of luciferase expression when cells were added to the culture medium of HEK293T-AhR-luc cells. The increase in luciferase expression level (RLU's) reflects the amount of PAHs in the blood of patients with CRC. By using the calibration curve we have determined the concentration of PAHs in nM. As it can be seen from the figure (figure 2B and 2C), for 6 out of 7 patients, the number of PAHs is higher than in the blood of healthy people. We believe that there is a correlation between the disease and the level of AhR ligands in the blood. It is impossible to determine whether a tumor produces endogenous ligands or this increase is due to the influx of PAHs from the outside. On the basis of the small group of samples, we cannot reach a final conclusion about the difference in the content of PAH in the blood, however, we assume that their level in patients with colorectal cancer is higher than that in healthy people.

3.5 The Concentration of XRE Ligands in the Tumor and Normal Tissue of Patients with Colon Cancer

The next question was to compare how the tumor transformation affects the level of ligands in the colon. For this, the effect of lysates of tumor tissue and adjacent normal mucosa on the level of luciferase expression was compared by adding the lysates into the culture medium of HEK293T-AhR-luc cells (figure 2D and E). It is clear, that the amount of AhR ligands is gets lower with increasing malignancy. However significant discrepancy between the level of luciferase activity in tumor tissue and the normal mucosa of the same patient was not registered in 4 out of 6 cases, whereas another two patients demonstrated a different character of dependency. We cannot prove the effect of tumor transformation on accumulation of PAHs in tumor tissues. Comparison of the levels of ligands in the normal mu-

DOI: https://doi.org/10.30564/jor.v1i1.410

cosa of patients with CRC has shown high heterogeneity (up to 3 times). We are unable to explain the nature and causes of this heterogeneity due to small cohort of patients.

4. Discussion

Huge progress has been made in the study of AhR signaling and the identification of new endogenous ligands, including the high-affinity ligand FICZ and kinurenin, both of which are tryptophan metabolites [11]. However, extensive studies of human AhR are required, since the functions of the receptor differ both in different species and in cells of different tissues, and also depending on the cellular environment [17]. Ligands of AhR not only have different affinities, but also a different nature - endogenous and exogenous, and can both activate and inhibit the receptor. The proposed reporter allows us to determine only the total concentration of the ligands of the AhR, there is no possibility to separate endogenous and exogenous ligands. That is, the activity of luciferase expression will reflect the level of activation of the AhR signaling pathway in response to the entire spectrum of ligands and allows us to observe the dynamics of the effect of therapy. The quantitative determination of the PAH by the method of mass spectroscopy in one sample reaches $ 1,000 and requires complex and complicated sample preparation. In this sense, the use of the reporter line repeatedly simplifies and reduces the cost of analysis, making it possible to make it accessible and widely used in both bio-medical and environmental studies. Cultivation of reporter cell line does not require expensive multicomponent media, the analysis is simple to do in many replications, and when cultivated, the cells are sufficiently resistant to the addition of the test samples to the culture medium. In order to check the activation of xenobiotic-metabolizing enzymes as a response to ligand binding to XRE, we have determined the expression level of AhR and its CYP1A surrogate target in reporter cell line. Our studies show an mRNA increase for CYP1A after FICZ (0.8 nM) treatment, while levels of AhR expression were similar (data not shown). However, as indicated above, a small number of samples does not allow making statistically reliable conclusions about differences in gene expression levels for patients with colorectal cancer compared with healthy ones. Therefore, the reporter strain can be used to test the content of PAH in various materials - water, milk, extracts of meat, fish, juices of vegetables and fruits, as well as in biological fluids - saliva, blood, urine.

We observe a significant increase of PAH level in the serum of patients with CRC independent of stage. We believe that we were the first to reveal such a difference in the levels of AhR ligands using a simple luciferase analysis. A similar pattern of differences was observed in the analysis of tissue lysates of tumors and adjacent mucosa - in 5 of 6 patients we have noted an increase of the PAH from 2-6 times. Proposed system does not allow to determine the origin of ligands (accumulation of endogenous or the deposition of exogenous).

Recognition of the potential for therapeutic use of AhR ligands required considerable experimental data and a long time to be confirmed due to well-known genotoxicity [14]. In recent reviews there is increasing evidence that the AhR and its ligands can be used as targets in the development of new drugs for antitumoral therapy [11, 14, 18].

The development of drugs that targeted AhR must take into account the selectivity property of modulators, manifested in the fact that the receptor ligand will serve as AhR agonist or antagonist depending on the tissue context [14, 19].

Thus, since it is known that AhR agonists enhance the growth of colon and stomach cancer cells, there is an assumption about the possible therapeutic role of selective modulators exhibiting antagonistic activity in this cellular context. In contrast, in most pancreatic tumors PAH inhibit cancer cell proliferation and anchorage-independent growth [20], suggesting that selective agonists will be effective for treating pancreatic cancer.

HEK293T-AhR-luc test system will allow to study the relationship between the concentration of PAHs and the degree of tumor malignancy (stage, tumor size, the presence of metastases) and serves for development of new selective modulators of AhR for cancer chemotherapy.

Conflicts of interest

The authors indicate no potential conflict of interests regarding the publication of this paper.

Acknowledgments

This work was supported by the grants from Russian Science Foundation (№ 14-50-00068).

Publication ethics

The paper received the ethical approval of St. Petersburg clinical scientific and practical center of specialized types of medical care (oncological) Ethics Committee.

References

[1] C.-E. Boström, P. Gerde, A. Hanberg, B. Jernström, C. Johansson, T. Kyrklund, A. Rannug, M.

DOI: https://doi.org/10.30564/jor.v1i1.410

Törnqvist, K. Victorin, R. Westerholm, Cancer risk assessment, indicators, and guidelines for polycyclic aromatic hydrocarbons in the ambient air, Environmental Health Perspectives, 2002, 110: 451-488.

[2] J. Ferlay, I. Soerjomataram, R. Dikshit, S. Eser, C. Mathers, M. Rebelo, D.M. Parkin, D. Forman, F. Bray, Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012, International Journal of Cancer, 2015, 136: E359-E386.

[3] D.W. Nebert, Aryl hydrocarbon receptor (AHR): "pioneer member" of the basic-helix/loop/helix per-Arnt-sim (bHLH/PAS) family of "sensors" of foreign and endogenous signals, Progress in Lipid Research, 2017, 67: 38-57.

[4] R. Evers, M. Kool, L. van Deemter, H. Janssen, J. Calafat, L.C. Oomen, C.C. Paulusma, R.P. Oude Elferink, F. Baas, A.H. Schinkel, P. Borst, Drug export activity of the human canalicular multispecific organic anion transporter in polarized kidney MDCK cells expressing cMOAT (MRP2) cDNA, The Journal of clinical investigation, 1998, 101: 1310-1319.

[5] S.K. Srivastava, S.C. Watkins, E. Schuetz, S.V. Singh, Role of glutathione conjugate efflux in cellular protection against benzo[a]pyrene-7,8-diol-9,10-epoxide–induced DNA damage, Molecular Carcinogenesis, 2002, 33: 156-162.

[6] Y. Shirasaka, R. Konishi, N. Funami, Y. Kadowaki, Y. Nagai, T. Sakaeda, S. Yamashita, Expression levels of human P-glycoprotein in In Vitro cell lines: correlation between mRNA and protein levels for P-glycoprotein expressed in cells, Biopharmaceutics & Drug Disposition, 2009, 30: 149-152.

[7] C. Wu, S. Yu, Q. Tan, P. Guo, H. Liu, Role of AhR in regulating cancer stem cell–like characteristics in choriocarcinoma, Cell Cycle, 2018, 17: 2309-2320.

[8] N.B. Marshall, N.I. Kerkvliet, Dioxin and immune regulation, Annals of the New York Academy of Sciences, 2010, 1183: 25-37.

[9] F.J. Quintana, D.H. Sherr, Aryl Hydrocarbon Receptor Control of Adaptive Immunity, Pharmacological Reviews, 2013, 65: 1148-1161.

[10] B. Stockinger, P.D. Meglio, M. Gialitakis, J.H. Duarte, The Aryl Hydrocarbon Receptor: Multitasking in the Immune System, Annual Review of Immunology, 2014, 32: 403-432.

[11] W. Bock Karl, Human and rodent aryl hydrocarbon receptor (AHR): from mediator of dioxin toxicity to physiologic AHR functions and therapeutic options, Biological Chemistry, 2017: 455.

[12] J.U. Kolluri S.K., Safe, S., Role of the aryl hydrocarbon receptor in carcinogenesis and potential as an anti-cancer drug target, Archives of Toxicology, 2017, 91: 17.

[13] G. He, T. Tsutsumi, B. Zhao, D.S. Baston, J. Zhao, S. Heath-Pagliuso, M.S. Denison, Third-Generation Ah Receptor–Responsive Luciferase Reporter Plasmids: Amplification of Dioxin-Responsive Elements Dramatically Increases CALUX Bioassay Sensitivity and Responsiveness, Toxicological Sciences, 2011, 123: 511-522.

[14] S. Safe, S.-O. Lee, U.-H. Jin, Role of the Aryl Hydrocarbon Receptor in Carcinogenesis and Potential as a Drug Target, Toxicological Sciences, 2013, 135: 1-16.

[15] O. van Tellingen, The importance of drug-transporting P-glycoproteins in toxicology, Toxicology Letters, 2001, 120: 31-41.

[16] O. Heinisch, Steel, R. G. D., and J. H. Torrie: Principles and Procedures of Statistics. (With special Reference to the Biological Sciences.) McGraw-Hill Book Company, New York, Toronto, London 1960, 481 S., 15 Abb.; 81 s 6 d, Biometrische Zeitschrift, 1962, 4: 207-208.

[17] X. Che, W. Dai, Aryl Hydrocarbon Receptor: Its Regulation and Roles in Transformation and Tumorigenesis, Current Drug Targets, 2019, 20: 1-10.

[18] I.A. Murray, A.D. Patterson, G.H. Perdew, Aryl hydrocarbon receptor ligands in cancer: friend and foe, Nature Reviews Cancer, 2014, 14: 801.

[19] S. Safe, C. Qin, A. McDougal, Development of selective aryl hydrocarbon receptor modulators for treatment of breast cancer, Expert Opinion on Investigational Drugs, 1999, 8: 1385-1396.

[20] A. Koliopanos, J. Kleeff, Y. Xiao, S. Safe, A. Zimmermann, M.W. Büchler, H. Friess, Increased arylhydrocarbon receptor expression offers a potential therapeutic target for pancreatic cancer, Oncogene, 2002, 21: 6059.

 DOI: https://doi.org/10.30564/jor.v1i1.410

BILINGUAL PUBLISHING CO.
Pioneer of Global Academics Since 1984

Journal of Oncology Research
https://ojs.bilpublishing.com/index.php/jor

ARTICLE

Psychological Intervention and Nursing Analysis of Gynecological Malignant Tumors during Chemotherapy

Yaning Liu[1*] Yan Zhang[2] Xiaoying Wang[3] Xinjuan Yang[4]

Baoji Maternal and Child Health Hospital, Baoji, Shanxi, 721000, China

ARTICLE INFO

Article history
Received: 16 March 2019
Accepted: 26 March 2019
Published Online: 30 April 2019

Keywords:
Gynecological malignant tumor
Chemotherapy
Psychological intervention
Clinical effect

ABSTRACT

Objectives: To explore the clinical effect of psychological intervention and nursing during the chemotherapy of gynecological malignant tumor. **Methods:** 120 patients with gynecologic malignancies were selected as subjects. According to the nursing method, these patients were divided into intervention group and control group, with 60 cases in each group. The patients in the control group were given routine care, and the patients in the observation group were given psychological intervention care on the basis of routine nursing. Before and after treatment, the anxiety and depression of the two groups were compared using the Self-rating Anxiety Scale (SAS) and the Self-rating Depression Scale (SDS). The satisfaction and adverse reactions of the two groups were compared. The results were statistically analyzed. **Results:** After nursing intervention, the anxiety and depression scores of the intervention group were lower than those of the control group ($P<0.05$). The incidence of nausea, vomiting and fatigue in the intervention group was significantly lower than that in the control group ($P<0.01$). There was no significant difference in the symptoms of diarrhea between the two groups ($P>0.05$). After the treatment, the satisfaction of the intervention group was significantly higher than that of the control group ($P<0.05$). **Conclusions:** During the chemotherapy of gynecological malignant tumor patients, psychological intervention nursing can alleviate the anxiety and depression of patients, improve the complications, and improve the satisfaction of patients. It is worthy of clinical application.

1. Introduction

Gynecological malignancies are common diseases that endanger women's health, which occur in various parts of the female genitalia. The most common are cervical cancer, endometrial cancer and ovarian cancer, and the highest mortality rate is ovarian epithelial cancer [1]. Chemotherapy plays an important role in the treatment of malignant tumors in customers. However, chemotherapy drugs have significant side effects. The most common nausea and vomiting, as well as fatigue, diarrhea, etc. [2]. This brings great pain to patients, and often leads to patients with depression and anxiety and other adverse emotions. Bad mood can aggravate the body's adverse reactions, thus forming a vicious cycle. Therefore, in the process of caring for such patients, the nursing staff not only needs to deal with the physiological discomfort of the patient, but also strengthen the psychological counseling

**Corresponding Author:*
Yaning Liu,
Baoji Maternal and Child Health Hospital, No. 15 Jing'er Road, Baoji, Shanxi, 721000, China;
E-mail: 1227209964@qq.com

DOI: https://doi.org/10.30564/jor.v1i1.689

of the patient. In this study, psychological intervention and nursing were adopted during the chemotherapy of gynecological malignant tumor, and good results were achieved.

2. Materials and Methods

2.1 General information

The study subjects were 120 patients with gynecologic malignancies who were treated in our hospital from May 2014 to May 2015. The age ranged from 28 to 55 years, with an average age of (37 ± 2.1) years. Patients diagnosed with nausea by pathology were rejected. Sixty-two patients with cervical cancer and 58 patients with ovarian cancer were treated with chemotherapy in our hospital. Patients were randomly divided into the intervention group and the control group, with 60 cases in each group. The patients in the intervention group were 28 to 53 years old, with an average of (37 ± 6.3) years, including 32 patients with cervical cancer and 28 patients with ovarian cancer. The patients in the control group ranged in age from 29 to 55 years, with an average of (37 ± 6.5) years, including 30 patients with ovarian cancer and 30 patients with cervical cancer. There were no significant differences in age, bed, severity of illness, and education level between the two groups (P>0.05), which were comparable.

2.2 Research Method

The control group received routine gynaecological care, and the intervention group added psychological nursing intervention on the basis of routine nursing, as follows:

Gynecological routine care: ① After admission to the hospital: Arrange bed, handle sanitation, measure temperature, pulse, breath, blood pressure. ② After the start of chemotherapy: The ward was inspected on time, and the patient's life and treatment response were closely observed. The amount of urine, the condition of the stool, the time and severity of adverse reactions were recorded, such as the number and amount of vomiting and diarrhea, and the mental state of the patient. In case of abnormal vaginal bleeding or pain in the lower abdomen, the patient should report to the doctor in time so as to take corresponding treatment measures in time. ③ Health care: keep the ward and bed clean, clean on time, disinfect regularly, bathe regularly, wash hair and cut nails. For oral care, rinse with 3% hydrogen peroxide. ④ Nutrition education for patients and their families, adjust the patient's diet, ensure a light, nutritious, high-protein diet, frequent small meals. When the patient has severe vomiting, he should replenish fluid and electrolyte in time to prevent water and electrolyte disturbance.

Psychological intervention care: ① After admission to the hospital: Warmly receive patients, strengthen communication with patients, eliminate patients' tension, and make them adapt to the hospital environment as soon as possible. The patient's personality, life habits and so on are understood, in order to take the individual nursing for different patients. ② Before chemotherapy begins: The nurse introduced the patient's role, implementation plan, and especially the adverse reactions that may occur in chemotherapy to the patient in detail. Taking a cured case as a typical example, the patient is motivated to meet the treatment with an optimistic and confident attitude. ③ After the start of chemotherapy: Patients will have varying degrees of adverse reactions. At this stage, patients are prone to anxiety, depression and other adverse emotions. Caregivers should increase their patience and care for the patient and use encouraging language to appease the patient's mood. During this period, the patient's mood is easily affected by the surrounding environment, especially the family's mood and attitude. Therefore, nursing staff should encourage patients' family members to care for patients, timely feedback of patients' adverse emotions, and encourage patients to overcome difficulties and adhere to treatment. The patient's sleep is understood, and if necessary, a drug such as diazepam is given to ensure the patient's rest. ④ The patient's psychology was assessed in a timely manner. When the patient has serious depression or anxiety, the psychologist should give professional counseling in time. ⑤ Hair loss care: Alopecia is a common adverse reaction during chemotherapy, which usually occurs 1 to 2 weeks after medication and often causes psychological disorders such as fear and anxiety. The nursing staff should explain to the patient that hair loss is temporary and the hair will regenerate after stopping the drug. The adverse effects of hair loss on the patient's psychology are minimized. ⑥ Before leaving the hospital: Medical staff should assist patients to do all kinds of work when leaving the hospital, including the preservation of outpatient medical records and discharge summary, so as to facilitate future treatment. Patients should strictly follow the doctor's advice, strengthen the influence, adjust the mood, and review in time.

2.3 Observation Standard

Before and after chemotherapy, the anxiety and depression of the two groups were compared using the Self-rating Anxiety Scale (SAS) and the Self-rating Depression Scale (SDS). The smaller the score, the better. The higher the score, the higher the level of anxiety and depression. Adverse reactions: The severity of nausea, vomiting, fatigue and diarrhea during chemotherapy were recorded, and were divided into three levels: mild, moderate and severe. Satisfaction survey: before leaving the hospital, the patients were asked to complete a satisfaction questionnaire, which

 DOI: https://doi.org/10.30564/jor.v1i1.689

was designed by our department, with 12 questions. The results were divided into three categories: very satisfied, satisfied and not satisfied. Satisfaction = (very satisfied number + satisfied number) / total number × 100%.

2.4 Statistical treatment

SPSS20.0 statistical software was used to process the data. Statistical analyses were performed using t-test for measurement data. The enumeration data was analyzed by chi-square test.

3. Results

There was no significant difference in the level of depression and anxiety between the two groups before chemotherapy (P> 0.05). After the end of chemotherapy, the anxiety and depression levels of the two groups were increased, but the scores of the intervention group were significantly lower than the control group (P<0.05). The difference was statistically significant (Table 1).

Table 1. Comparison of anxiety and depression between the two groups before and after intervention (x ± s)

Group	n	SAS score		SDS score	
		Before intervention	After intervention	Before intervention	After intervention
Intervention group	60	38.23 ± 5.20^{m}	38.16 ± 5.23^{m}	38.32 ± 7.28^{x}	39.17 ±5.16^{y}
Control group	60	37.89 ± 7.35	42.16 ± 642	38.39 ± 6.35	42.41 ± 4.39
T		0.29	3.71	0.06	3.70
P		>0.05	<0.05	>0.05	<0.05

Note: Compared with the control group, nP<0.05, yP<0.05, the difference was statistically significant. mP>0.05, xP>0.05, the difference was not statistically significant.

The occurrence of adverse reactions: The degree of nausea and vomiting and fatigue in the intervention group were lower than those in the control group (P<0.01). The severity of diarrhea was not significantly different between the two groups (P > 0.05) (Table 2).

Table 2. Comparison of adverse reactions between the two groups

Group	n	Nausea and vomiting			Fatigue and lack of strength			Diarrhea		
		Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe
Intervention tion group	60	32	15	13^{a}	48	14	8^{b}	43	9	8^{c}
Control group	60	11	30	29	18	31	21	40	11	9
X^2		9.38			7.68			0.07		
P		<0. 01			<0. 01			>0.05		

Note: Compared with the control group, aP<0.01, bP<0.01, the difference was statistically significant. cP>0.05, the difference was not statistically significant.

When leaving the hospital, the satisfaction of the intervention group was higher than that of the control group (P<0.05) (Table 3).

Table 3. Comparison of satisfaction between the two groups /n(%)

	n	Very satisfied	Satisfied	Not satisfied	Satisfaction
Intervention group	60	24(40.008)	34(56.67)	2(3.33)	96.67*
Control group	60	14(23.33)	34(56.67)	12(20.00)	80.00
χ2					8.09
P					<0.05

Note: Compared with the control group, *P<0.05, the difference was statistically significant.

4. Discussion

Gynecologic malignancies are a serious disease that seriously threatens women's health and life. Compared with other diseases in the clinic, the psychological impact of malignant tumors on patients is more obvious [3-4]. Many studies have shown that [5-7], patients with nausea are often accompanied by psychological disorders such as anxiety and depression, which seriously affect the quality of life of patients. Many patients have insufficient knowledge of malignant tumors and often blindly believe that cancer is incurable. Therefore, some patients give up treatment. Surgery and chemotherapy are the basic means of treating gynecological malignancies. Due to the cytotoxic effect of chemotherapy drugs, clinical patients often have varying degrees of toxic and side effects and organ damage. Common adverse reactions are mainly gastrointestinal reactions, fatigue, bone marrow suppression, infection, hair loss, etc. [8-9]. Adverse reactions can aggravate the mood of patients with rejection therapy. In clinical, some patients even interrupt chemotherapy because they cannot tolerate these reactions, which seriously affects the therapeutic effect. Therefore, the comprehensive nursing for the patients with chemotherapy is the guarantee to complete the chemotherapy plan.

In the course of chemotherapy for malignant tumors, caregivers are most closely related to patients. The patient's problem should be promptly replied and processed. This is especially important for the care of gastrointestinal reactions, myelosuppression, infection, bleeding, etc. [10]. In addition, the role of psychological intervention care in the treatment of patients with malignant tumors has gradually received attention. Previous studies have shown that its application in clinical practice is obvious [11-12]. Patients with gynecologic malignancies are female groups and psychological characteristics are noted. Studies have shown that women are more prone to psychological dis-

DOI: https://doi.org/10.30564/jor.v1i1.689

orders of anxiety and depression due to the influence of family and social roles [13]. Chemotherapy also has a greater physical impact on the patient. For example, hair loss often leads to fear, feelings of despair, and the psychology of rejection of chemotherapy. Therefore, it is very important to give psychological intervention care during chemotherapy for patients with gynecologic malignancies. This study explores this issue and achieves significant results. After psychological care, the patient's depression and other adverse reactions were improved and satisfaction was significantly improved. This is basically consistent with the study of Jinya You [15]. The main reason is that the psychological state has a great impact on the patient's condition. Anxiety and depression can aggravate adverse reactions, which in turn aggravate psychological barriers. Psychological nursing can improve patients' bad mood and reduce the occurrence of adverse reactions. Patient satisfaction will naturally increase accordingly.

The deficiency of this study is that in order to reduce the pain of patients, the study of bone marrow transplantation was not involved. The sample size is small and there may be errors. As a result, the sample size needs to be further expanded.

To sum up, during the chemotherapy of gynecological malignant tumor patients, psychological intervention nursing can alleviate the anxiety and depression of patients, improve the complications, and improve the satisfaction of patients. It is worthy of clinical application.

References

[1] Xiyuan Feng, Shujuan Liao, Biru Luo. Investigation and Analysis of Self-Care Ability, Self-Care Behavior and Health Education Needs in Patients with Gynecologic Cancer during Chemotherapy [J]. Chinese nursing research. 2013(7): 2202-2204.

[2] Manman Cui. Clinical Manifestations and Treatment Strategies of Adverse Reactions after Chemotherapy in Gynecological Cancer Patients [J]. Laboratory Medicine and Clinical.2014 (3): 292-293.

[3] Feipeng Wang, Xinxuan Zhang, Xiaochun Jiang, He He. Analysis of Negative Emotions and Its Influencing Factors in Hospitalized Patients with Gynecologic Tumors [J]. Journal of International Psychiatry, 2015, 03(03):78-79.

[4] Rong Chen, Xueling Weng, Jing Xu, Lizhen Mo, Weihua Xue. Effect of Psychological Nursing Intervention on Patients with First Chemotherapy for Gynecological Tumors [J]. Journal of Qilu Nursing, 2015(2): 118-119.

[5] Yun Wang, Nan Qin, Li Cheng, Jun Lei. Research Progress on Sleep Disorders in Patients with Gynecological Malignant Tumors [J]. Chinese nursing research. 2013 (1): 193-19

[6] Xiuyu Li. Malignant Tumors and Depression [J]. Clinical Journal of Chinese Medicine. 2012(13): 1-4.

[7] Yuqiong Cai, Zehua Wang, Weihong Dong, Denghua Liu. Investigation on Anxiety and Depression in Patients with Gynecological Malignant Tumors [J]. Neural Injury and Functional Reconstruction. 2011(4): 269-271.

[8] Jinfeng Zhao. Effect of Preoperative Individualized Psychological Nursing Intervention on Stress Response in Patients Undergoing Gynecologic Tumor Surgery [J]. Nursing Practice and Research. 2013(18): 113-115.

[9] Dongyan Zheng, Ying Yu, Liqin Wang, Guilan Yan. Analysis of Psychological State and Influencing Factors of Patients with Gynecological Malignant Tumors and Countermeasures [J]. Journal of Modern Nursing. 2006(1): 56-58.

[10] Fengxia Hu, Yahui Li, Pingping Cheng, Ling Peng. Application of Brand Nursing in Gynecological Tumor Quality Nursing Service [J]. Today Nurse: Academic Edition. 2013(4): 110-11.

[11] Lina Gong. Application Value of Health Education and Psychological Nursing in the Nursing of Gynecologic Oncology Patients [J]. Laboratory Medicine and Clinical.2014 (14): 2022-2024.

[12] Yan Shen, Renyin Huang. Effect of Psychological Nursing on Postoperative Psychological Status of Patients with Gynecologic Tumors [J]. Chinese Journal of Practical Nursing. 2011(27): 47-48.

[13] Hui Zhu, Weilan Yao, Yingrui Liu, Jun Liu, Dan Shi. Psychological Nursing of Patients with Gynecologic Cancer [J]. Guide of China Medicine. 2013(18)309-310.

[14] Chunli Cui, Ren Gao, Zhaomin Yan. Preoperative Negative Emotion Analysis and Nursing Strategy for Patients with Gynecologic Tumors [J]. China Clinical Practical Medicine.2015 (1): 69-70.

[15] Jinya You, Mingzhu Chen. Effect of Comprehensive Nursing Intervention on Psychological Status and Quality Of Life in Patients with Gynecologic Cancer Chemotherapy [J]. Laboratory Medicine and Clinic.2014 (22): 3222-3223.

 DOI: https://doi.org/10.30564/jor.v1i1.689

BILINGUAL PUBLISHING CO.
Pioneer of Global Academics Since 1984

Journal of Oncology Research
https://ojs.bilpublishing.com/index.php/jor

REVIEW

Interaction between Immunotherapy and Radiotherapy

Yasemin Benderli Cihan*

Kayseri Education and Research Hospital, Department of Radiation Oncology, 38010, Kayseri, Turkey

ARTICLE INFO

Article history
Received: 20 September 2019
Accepted: 26 September 2019
Published Online: 30 September 2019

Keywords:
Immunotherapy
Radiotherapy

ABSTRACT

In recent years, treatment methods on immune checkpoints have emerged as promising novel therapeutic modalities against cancer as a result of studies focusing on elucidation of immune micro-environment. Immunotherapy has now become an established treatment in some cancers. [1-2] This has led the need for investigation of biomarkers which allow determining effectiveness of immunotherapies and patient groups which will most benefit from these therapies. In previous studies, it was suggested that programmed death receptor-1 (PD-1) and programmed death ligand-1 (PD-L1) expressions could be predictive biomarkers in cancers. PD-1 is a transmembrane protein present in macrophages, myeloid dendritic cells, B cells, epithelial cells and vascular endothelial cells, which limits and inhibits immunological activation in activated T cells. Blocking PD-1/PD-L1 interaction promises hope in the cancer treatment. In clinical studies, it was shown that targeted PD-1/PD-L1 therapy alone or in combination with other modalities is beneficial in advanced cancers with aggressive behavior. It was shown that overexpression of PD-1 present in tumoral micro-environment is associated to poor prognosis in gastric cancer, breast cancer, ovarian cancer, kidney, pancreas and lung cancers and in melanoma. [1-5]

1. Introduction

Radiotherapy exerts its effect by enhancing death in irradiated tumor cells and elimination inflammation at tumor micro-environment. In other words, it exerts its effect by inducing antigen expression on tumor cells and activating lymphocytes. [1,2] Radiation can induce either inflammatory or anti-inflammatory reactions depending on dose and fractionation. In a study, Patel et al. assessed activated and enhancing T cell infiltration in high-dose (15-20 Gy;1-3 fractions) and low-dose (3-5 Gy;4-5 fractions) radiotherapy regimens. Authors emphasized that T cell infiltration was higher resulting in delay in tumor growth in high-dose regimens. [4] Dewan et al. investigated different dose and schemes (20 Gy/one fraction; 24 Gy/3 fractions; 30 Gy/5 fractions) on two poorly immunogenic tumors. Authors found that anti-tumor activity was higher in those received 24 Gy in 3 fractions. [5]

2. Study and Test

The success of blockade of PD-1/PD-L1 pathway in combination with radiotherapy in killing tumors in

**Corresponding Author:*
Yasemin Benderli Cihan,
Kayseri Education and Research Hospital, Department of Radiation Oncology, 38010, Kayseri, Turkey;
Email: cihany@erciyes.edu.tr

DOI: https://doi.org/10.30564/jor.v1i1.1263

preclinical studies has encouraged researchers for testing these agents in some tumors. In preclinical studies, it was shown that concomitant use of immunotherapy with radiotherapy was more effective than sequential administration. Currently, phase 1 and 2 clinical trials investigating combination of targeted PD-1 and PD-L1 blockage with chemotherapy (NCT02305186) and radiotherapy (NCT02303990, NCT02311361, NCT02298946) are ongoing. In published series, controversial outcomes have been reported regarding timing of immunotherapy in accurate dose and fractionation of radiotherapy. Radiation necrosis is most common adverse effect of radiotherapy and immunotherapy, which is difficult to manage [2,4]

3. Conclusion

In conclusion, programmed death pathway is an important immune control step that functions in late phases of inflammation. Targeted PD-1/PD-L1 therapy in combination with radiotherapy may enable promising results in cancer patients. It is now unclear which radiotherapy technique or regiment will be effective together with immunotherapy. It seems very important to produce a synergism between radiation dose and immune system. Further prospective, randomized studies with large sample size are needed for this purpose.

References

[1] Kroeze SG, Fritz C, Hoyer M, et al. Toxicity of concurrent stereotactic radiotherapy and targeted therapy or immunotherapy: A systematic review. Cancer Treat Rev. 2017, 53: 25-37.
DOI: 10.1016/j.ctrv.2016.11.013

[2] Seyedin SN, Schoenhals JE, Lee DA, et al. Strategies for combining immunotherapy with radiation for anticancer therapy.Immunotherapy. 2015, 7(9): 967-980.
DOI: 10.2217/imt.15.65

[3] De Wolf K, Kruse V, Sundahl N, et al. A phase II trial of stereotactic body radiotherapy with concurrent anti-PD1 treatment in metastatic melanoma: evaluation of linical and immunologic response. J Transl Med. 2017, 15(1): 21.
DOI: 10.1186/s12967-017-1123-x

[4] Patel KR, Lawson DH, Kudchadkar RR, et al. Two heads beter than one? Ipilimumab immunotherapy and radiation therapy for melanoma brain metastases. NeuroOncol, 2015, 17(10): 1312–21.

[5] Dewan MZ, Galloway AE, Kawashima N, et al. Fractionated but not single-dose radiotherapy induces an immune-mediated abscopal effect when combined with anti-CTLA-4 antibody. Clin Cancer Res, 2009, 15: 5379–88.

 DOI: https://doi.org/10.30564/jor.v1i1.1263

Author Guidelines

This document provides some guidelines to authors for submission in order to work towards a seamless submission process. While complete adherence to the following guidelines is not enforced, authors should note that following through with the guidelines will be helpful in expediting the copyediting and proofreading processes, and allow for improved readability during the review process.

Ⅰ. Format

- Program: Microsoft Word (preferred)
- Font: Times New Roman
- Size: 12
- Style: Normal
- Paragraph: Justified
- Required Documents

Ⅱ. Cover Letter

All articles should include a cover letter as a separate document.

The cover letter should include:

- Names and affiliation of author(s)

The corresponding author should be identified.

Eg. Department, University, Province/City/State, Postal Code, Country

- A brief description of the novelty and importance of the findings detailed in the paper

Declaration

v Conflict of Interest

Examples of conflicts of interest include (but are not limited to):

- Research grants
- Honoria
- Employment or consultation
- Project sponsors
- Author’s position on advisory boards or board of directors/management relationships
- Multiple affiliation
- Other financial relationships/support
- Informed Consent

This section confirms that written consent was obtained from all participants prior to the study.

- Ethical Approval

Eg. The paper received the ethical approval of XXX Ethics Committee.

- Trial Registration

Eg. Name of Trial Registry: Trial Registration Number

- Contributorship

The role(s) that each author undertook should be reflected in this section. This section affirms that each credited author has had a significant contribution to the article.

1. Main Manuscript

2. Reference List

3. Supplementary Data/Information

Supplementary figures, small tables, text etc.

As supplementary data/information is not copyedited/proofread, kindly ensure that the section is free from errors, and is presented clearly.

Ⅲ. Abstract

A general introduction to the research topic of the paper should be provided, along with a brief summary of its main results and implications. Kindly ensure the abstract is self-contained and remains readable to a wider audience. The abstract should also be kept to a maximum of 200 words.

Authors should also include 5-8 keywords after the abstract, separated by a semi-colon, avoiding the words already used in the title of the article.

Abstract and keywords should be reflected as font size 14.

Ⅳ. Title

The title should not exceed 50 words. Authors are encouraged to keep their titles succinct and relevant.

Titles should be reflected as font size 26, and in bold type.

Ⅳ. Section Headings

Section headings, sub-headings, and sub-subheadings should be differentiated by font size.

Section Headings: Font size 22, bold type

Sub-Headings: Font size 16, bold type

Sub-Subheadings: Font size 14, bold type

Main Manuscript Outline

Ⅴ. Introduction

The introduction should highlight the significance of the research conducted, in particular, in relation to current state of research in the field. A clear research objective should be conveyed within a single sentence.

Ⅵ. Methodology/Methods

In this section, the methods used to obtain the results in the paper should be clearly elucidated. This allows readers to be able to replicate the study in the future. Authors should ensure that any references made to other research or experiments should be clearly cited.

Ⅶ. Results

In this section, the results of experiments conducted should be detailed. The results should not be discussed at length in

this section. Alternatively, Results and Discussion can also be combined to a single section.

Ⅷ. Discussion

In this section, the results of the experiments conducted can be discussed in detail. Authors should discuss the direct and indirect implications of their findings, and also discuss if the results obtain reflect the current state of research in the field. Applications for the research should be discussed in this section. Suggestions for future research can also be discussed in this section.

Ⅸ. Conclusion

This section offers closure for the paper. An effective conclusion will need to sum up the principal findings of the papers, and its implications for further research.

Ⅹ. References

References should be included as a separate page from the main manuscript. For parts of the manuscript that have referenced a particular source, a superscript (ie. [x]) should be included next to the referenced text.

[x] refers to the allocated number of the source under the Reference List (eg. [1], [2], [3])

In the References section, the corresponding source should be referenced as:

[x] Author(s). Article Title [Publication Type]. Journal Name, Vol. No., Issue No.: Page numbers. (DOI number)

Ⅺ. Glossary of Publication Type

J = Journal/Magazine

M = Monograph/Book

C = (Article) Collection

D = Dissertation/Thesis

P = Patent

S = Standards

N = Newspapers

R = Reports

Kindly note that the order of appearance of the referenced source should follow its order of appearance in the main manuscript.

Graphs, Figures, Tables, and Equations

Graphs, figures and tables should be labelled closely below it and aligned to the center. Each data presentation type should be labelled as Graph, Figure, or Table, and its sequence should be in running order, separate from each other.

Equations should be aligned to the left, and numbered with in running order with its number in parenthesis (aligned right).

Ⅻ. Others

Conflicts of interest, acknowledgements, and publication ethics should also be declared in the final version of the manuscript. Instructions have been provided as its counterpart under Cover Letter.

About the Publisher

Bilingual Publishing Co. (BPC) is an international publisher of online, open access and scholarly peer-reviewed journals covering a wide range of academic disciplines including science, technology, medicine, engineering,education and social science. Reflecting the latest research from a broad sweep of subjects, our content is accessible worldwide – both in print and online.

BPC aims to provide an analytics as well as platform for information exchange and discussion that help organizations and professionals in advancing society for the betterment of mankind. BPC hopes to be indexed by well-known databases in order to expand its reach to the science community, and eventually grow to be a reputable publisher recognized by scholars and researchers around the world.

BPC adopts the Open Journal Systems, see on http://ojs.bilpublishing.com

Database Inclusion

Asia & Pacific Science Citation Index

Creative Commons

China National Knowledge Infrastructure

Google Scholar

Crossref

MyScienceWork

Bilingual Publishing Co. is a company registered in Singapore in 1984, whose office is at 12 Eu Tong Sen Street, #08-169, Singapore 059819, enjoying a high reputation in Southeast Asian countries, even around the world.

BILINGUAL PUBLISHING CO.
Pioneer of Global Academics Since 1984

Tel: +65 65881289
E-mail: contact@blipublishing.Com
Website: www.Blipublishing.Com

ISSN 2630-5267 01
9 772630 526199