Hyperthermic Intraperitoneal Chemotherapy for Recurrent Nephroblastoma in Children

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ABSTRACT

Objective: To investigate the clinical efficacy and safety of hyperthermic intraperitoneal chemotherapy (HIPEC) in the treatment of recurrent nephroblastoma in children.

Study Design: Randomised controlled trial.

Place and Duration of Study: Department of Oncology, Baoding Children's Hospital, from August 2018 to November 2021.

Methodology: Sixty children with recurrent nephroblastoma treated by HIPEC in the Department of Surgical Oncology were analysed and divided into group A and group B, according to different perfused drugs. Additionally, 30 children without a history of HIPEC were selected as the control group (group C). The changes in routine blood indices, albumin, and hepatic and renal function of the three groups were observed before and after treatment. The clinical efficacy, frequency of adverse reactions, as well as 6-month and 1-year tumour recurrence in the three groups were compared.

Results: The efficacy in groups A and B was significantly higher than that in group C ($p<0.05$). Changes in routine blood indices, albumin, and hepatic and renal function showed no statistically significant differences among the three groups during each observation period after treatment (all $p>0.05$). No significant differences were found in the incidence of adverse reactions among the three groups during treatment (all $p>0.05$). Six months after treatment, the tumour recurrence rate presented no significant differences among the three groups. However, at 12-months after treatment, the recurrence rate in groups A and B was lower than that in group C ($p<0.05$).

Conclusion: For children with recurrent nephroblastoma, intraoperative HIPEC has little impact on the body, can significantly improve the effectiveness and reduce the recurrence rate, and does not increase the adverse reactions.

Key Words: *Children, Recurrence, Nephroblastoma, Hyperthermic perfusion.*

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INTRODUCTION

Nephroblastoma, also known as Wilms' tumour (WT), is a common renal malignancy in children following neuroblastoma, with the second incidence among primary intra-abdominal malignant tumours in children, accounting for more than 90%.[1] About 75% of nephroblastomas occur before 5 years of age; the peak age is 2-3 years. There is no significant difference in the incidence between boys and girls, but the age of onset in girls is higher.[2] In most patients, a palpable abdominal mass is an initial symptom,[3] and some patients present symptoms such as haematuria, fever, urinary tract infection, varicocele, hypertension or hypotension, anaemia, *etc*. At present surgery, chemotherapy, and radiotherapy constitute the basic treatment for nephroblastoma.

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Experts agree that decompression surgery should be performed first, and then followed by radiotherapy, chemotherapy, and adjuvant therapy. In the past, the long-term survival rate of patients with nephroblastoma was less than 30%, and now the overall cure rate has exceeded 90%.[4] However, due to incomplete resection and delayed postoperative radiotherapy and chemotherapy, children with advanced nephroblastoma often suffer from postoperative recurrence and metastasis, resulting in a decline in their survival rate.

In recent years, the use of hyperthermia therapy for malignant tumours has become an important means in the field of tumour therapy. It is considered after surgery, radiotherapy, chemotherapy, and biotherapy. Although the 5-year survival rate of nephroblastoma in children has been increased to 90% through standardised combined treatment, there is still about 15% recurrence rate. The invasive growth and drug resistance of recurrent nephroblastoma lead to difficulties in resection and chemotherapy of recurrent nephroblastoma, so the prognosis is poor. The 2-year tumour-free survival rate is 43-70%. The treatment of recurrent nephroblastoma is the current research focus, and there is little research on recurrent nephroblastoma.[5,6] The aim of this study was to evaluate the effectiveness and safety of hyperthermic intraperitoneal

chemotherapy (HIPEC) in children with recurrent nephroblastoma and to provide a reference for the relevant clinical application.

METHODOLOGY

The study was approved by the Institutional Ethics Committee of the hospital (No.: 2018-02). Written informed consent were obtained from all participants. Ninety children with recurrent nephroblastoma, admitted to the Department of Surgical Oncology of Baoding Children's Hospital from August 2018 to November 2021, were selected for this study. Patients were randomly divided into three groups using random number table methods, Group A and Group B were treated with different HIPEC, and Group C had not been treated with HIPEC. The inclusion criteria were a child meeting the diagnostic criteria of nephroblastoma in Chinese'Expert Consensus on Diagnosing and Treating Pediatric Wilms' Tumour,[5] the primary tumour having poor prognosis type of COG Ⅱ and Ⅲ of patients with recurrent nephroblastoma,[6-8] and the guardians accepting the study and signing the informed consent. The exclusion criteria were complicated with other malignant tumours, and allergic to the medicines used.

All patients underwent resection of recurrent lesions by the same surgical team after admission. Intraoperatively, group A was treated with normal saline + 20 ml/L cisplatin 50 ml/m^2 (body surface area) + doxorubicin 15/m^2 (body surface area) by circulating perfusion at 41℃ for 60 minutes. Group B underwent normal saline + ifosfamide 1 g/m^2 (body surface area) + doxorubicin 15/m^2 (body surface area) by circulating perfusion at 41℃ for 60 minutes. Group C received no HIPEC. Postoperatively, the three groups were all given 4-6 cycles of ICE chemotherapy regimen (ifosfamide + carboplatin + etoposide), because group A and group B were treated with different HIPEC. In addition to routine chemotherapy, they were taken as the experimental groups, and group C was treated with chemotherapy only, so it was used as the observation (control) group.

The clinical efficacy was evaluated according to the criteria published by the Union for International Cancer Control (UICC) and the World Health Organization (WHO). The efficacy response to treatment was assessed *via* complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD), overall response rate = (CR + PR)/total cases × 100%.

Routine blood indices including white blood cell (WBC), red blood cell (RBC), haemoglobin (HB) and platelet (PLT), as well as biochemical indices including albumin, hepatic function (alanine aminotransferase, aspartate aminotransferase), and renal function (creatinine, urea nitrogen) of the three groups, were observed before surgery and 2 hours(h), 24 h and 72 h after HIPEC. In addition, adverse reactions during treatment: fever, nausea and vomiting, myelosuppression, haematuria and cystitis, as well as postoperative pulmonary infection were recorded.

A specially assigned person followed up all patients for 1 year after treatment. Tumour recurrence of the three groups was evaluated at 6-month follow-up and at the end of follow-up.

Statistical analysis was carried out using SPSS 22.0. The data were tested for normal distribution by Shapiro-Wilk(*S-W*) method. Normal distribution data were expressed by median and IQR and analysed by one-way ANOVA. The skewed distribution data were expressed by median (IQR); non-normal distribution data used Kruskal-Wallis test. The enumeration data were expressed as *n* (%), and compared between groups using the X^2 test. A value of $p<0.05$ was considered statistically significant.

RESULTS

In group A, there were fourteen boys (46.6%) and sixteen girls (53.3%) with an average age of 6.70 ± 3.27 years. Twenty (66.6%) children with left-sided nephroblastoma, ten (33.3%) with right-sided nephroblastoma, and intra-abdominal metastasis were fourteen in eight (26.6%) children. In group B, seventeen boys (56.6%) and thirteen girls (43.3%) were included, the average age was 6.60 ± 3.36 years, seventeen (56.6%) children had left-sided nephroblastoma, thirteen (43.3%) has right-sided nephroblastoma, with intra-abdominal metastasis in nine (30%) children. Group C enrolled thirteen boys (43.3%) and seventeen (56.6%) girls with an average age of 6.27 ± 3.27 years, fourteen (46.6%) left--sided nephroblastoma, sixteen (53.3%) right-sided nephroblastoma, and intra-abdominal metastasis in eleven (36.6%). The data of the three groups were balanced and comparable, without statistically significant differences ($p>0.05$).

After treatment, the efficacy in group A (90.00%) and B (86.66%) was higher than that in group C (66.67% $X^2=6.237$, $p=0.044$). Before and after treatment, each routine blood and biochemical indices showed no statistically significant differences among the three groups ($p>0.05$). as seen in Table I.

During treatment, adverse reactions occurred in all three groups. The incidence of cystitis was the highest in group A (13.33%) and group C (13.33%), and the incidence of haematuria was the highest in group B (13.33%). However, no statistically significant differences were found in the incidence of adverse reactions among the three groups ($X^2=0.278$, $p=0.875$).

The 6-month follow-up after treatment showed no statistically significant differences in the recurrence rate among the three groups ($p>0.05$). The follow-up after 1 year of treatment demonstrated that the recurrence rate in group C was significantly higher than that in group A and B ($p=0.026$), as displayed in Table II.

DISCUSSION

At present, nephroblastoma is one of the most common renal malignant solid tumours in children, with unknown aetiology. Most children present as an asymptomatic abdominal mass, and others due to clinical manifestations such as abdominal pain, microscopic haematuria or gross haematuria. These clinical manifestations are not typical for the diagnosis of nephroblastoma, which is easy to lead to delayed diagnosis. Most patients were in the late clinical stage when diagnosed, with poor treatment effect and easy to relapse after treatment. At present, there is a clinical consensus on its treatment regimen.

Table I: Comparison of routine blood and biochemical indices among three groups (Median, IQR).

Item		Group A (n = 30)	Group B (n = 30)	Group C (n = 30)	t square	p*
WBC (10^9/L)	Before surgery	6.80(2.12)	6.93(2.22)	7.34(2.12)	0.635	0.728
	2 h after surgery	7.83(2.09)	7.96(2.22)	8.37(2.17)	0.467	0.792
	24 h after surgery	5.73(2.12)	5.90(2.22)	6.31(2.12)	0.493	0.781
	72 h after surgery	5.18(2.22)	5.31(1.88)	5.68(2.22)	0.469	0.791
RBC (10^{12}/L)	Before surgery	4.42(1.15)	4.52(1.29)	4.47(1.08)	0.121	0.941
	2 h after surgery	5.13(1.12)	5.13(1.19)	5.11(0.97)	0.055	0.973
	24 h after surgery	3.77(1.44)	3.91(1.64)	3.86(1.08)	0.116	0.944
	72 h after surgery	4.14(1.21)	4.19(1.28)	4.28(1.01)	0.037	0.982
HB (g/L)	Before surgery	97.50(25.25)	98.00(17.00)	98.00(18.25)	0.137	0.934
	2 h after surgery	94.50(16.25)	94.50(8.25)	96.00(12.50)	0.541	0.763
	24 h after surgery	92.00(13.75)	91.00(10.50)	93.00(11.75)	0.331	0.847
	72 h after surgery	88.00(12.50)	87.00(10.75)	90.00(10.25)	0.984	0.611
PLT (10^9/L)	Before surgery	197.50(26.25)	201.50(17.00)	200.50(17.25)	0.050	0.975
	2 h after surgery	123.00(17.75)	123.00(16.25)	124.50(18.00)	0.356	0.837
	24 h after surgery	102.50(26.25)	103.00(17.50)	103.00(16.25)	0.073	0.964
	72 h after surgery	121.00(26.25)	125.50(18.00)	124.50(17.00)	0.214	0.898
Albumin (g/L)	Before surgery	49.05(8.70)	49.25(8.70)	48.85(8.50)	0.095	0.954
	2 h after surgery	48.85(8.70)	49.05(8.70)	49.35(8.50)	0.082	0.960
	24 h after surgery	42.55(8.88)	42.75(8.88)	42.35(8.50)	0.053	0.974
	72 h after surgery	37.55(8.25)	37.75(8.15)	37.50(8.20)	0.064	0.969
Alanine aminotransferase (U/L)	Before surgery	60.25(8.05)	60.45(8.05)	60.15(8.38)	0.223	0.894
	2 h after surgery	112.85(8.70)	113.30(9.03)	109.35(8.75)	2.198	0.333
	24 h after surgery	183.95(12.27)	183.15(10.23)	180.95(8.22)	2.389	0.303
	72 h after surgery	192.65(11.15)	192.85(9.93)	189.55(11.03)	0.311	0.856
Aspartate aminotransferase (U/L)	Before surgery	43.75(7.33)	43.95(7.78)	43.70(7.50)	0.042	0.979
	2 h after surgery	88.00(6.50)	89.45(5.60)	87.15(5.42)	0.453	0.797
	24 h after surgery	135.90(7.05)	136.10(6.20)	134.75(6.15)	0.927	0.629
	72 h after surgery	113.50(6.40)	113.40(5.40)	110.15(5.48)	3.549	0.170
Creatinine (μmol/L)	Before surgery	75.80(10.05)	76.00(8.50)	73.60(6.65)	0.961	0.619
	2 h after surgery	81.10(11.67)	81.40(8.50)	77.75(6.60)	1.611	0.447
	24 h after surgery	84.40(10.05)	84.60(8.50)	82.20(6.30)	0.979	0.613
	72 h after surgery	74.50(9.98)	74.70(8.60)	72.30(6.65)	0.873	0.646
Urea nitrogen (mmol/L)	Before surgery	5.20(7.53)	5.30(6.80)	4.00(4.55)	0.622	0.733
	2 h after surgery	8.20(8.00)	8.30(7.10)	6.65(5.38)	1.274	0.529
	24 h after surgery	8.50(8.00)	8.00(6.95)	6.80(5.37)	0.898	0.638
	72 h after surgery	6.60(7.00)	6.10(6.65)	5.25(4.58)	0.480	0.787

*Note: *All applied Kruskal-Wallis test.*

Table II: Comparison of recurrence among three groups [n (%)].

Group	6-month follow-up	12-month follow-up
Group A (n = 30)	1 (3.33)	3 (10.00)
Group B (n = 30)	1 (3.33)	2 (6.67)
Group C (n = 30)	3 (10.00)	9 (30.00)
c^2	1.694	7.274
p	0.429	0.026*

*Note: *X^2 test.*

With the improvement in medical management, the overall survival rate of nephroblastoma has reached more than 75% in China and 90% in developed countries after surgery and chemoradiotherapy. Although the survival rate of children with nephroblastoma has greatly improved after multidisciplinary treatment, the recurrence rate after treatment is still about 15%, and the survival rate of patients with recurrence after secondary treatment is only about 30%.[9] Therefore, how to treat recurrent nephroblastoma is the current research highlights.

In 1886, Dr. Bush reported for the first time that hyperthermia therapy could regress tumours. After more than a century of research, it has been confirmed that hyperthermia therapy denatures cell membrane proteins at the molecular level, affects the synthesis and proliferation of DNA/RNA in tumour cells, and then kills tumour cells, especially sensitive to tumour cells at S and M stages. The heat shock protein produced by cell necrosis is released into the blood circulation and activates the body's immune system, thus eliminating tumour cells in the body. Therefore, clinically, some scholars believe that hyperthermia therapy is one of the most effective methods to treat malignant tumours.[10,11]

Cisplatin is the main chemotherapeutic agent for a variety of abdominal malignant solid tumours in children. It is considered an ideal intraperitoneal chemotherapeutic drug

because of its low liposolubility. The thermal effect produced by hyperthermic perfusion can improve the sensitivity of tumour cells to cisplatin, resulting in doubled therapeutic effect. The mechanisms of hyperthermic perfusion are multifile Cisplatin has high molecular weight and low liposolubility, so it is not likely to penetrate the thoracic (abdominal) membrane, resulting in a small amount of medicines entering the blood circulation, and low systemic toxicity and side effects. In addition, it can form and maintain a medicine concentration higher than the plasma concentration in the body cavity. Moreover, it has strong penetration and can penetrate into the tumour to kill deep tumour cell. The blood vessels of tumour tissue lack smooth muscle and have poor expansibility, so hyperthermic perfusion can destroy the blood vessels and cut-off the blood supply of tumours. It has been shown that the perfusion solution above 42℃ for one hour can significantly kill tumour cells, and increase the vascular permeability of tumour tissues, which is conducive to the infiltration of chemotherapeutic drugs into tumour cells to kill them. With the scouring effect, hyperthermic perfusion can flush out and expel tumour cells from the body cavity.[12-14] At present, cisplatin is most commonly used in HIPEC, and the best dose and time is 70 mg/m^2 at 42℃ for 60 minutes. Zivanovic and other studies also confirmed that the pharmacokinetic and pharmacodynamic characteristics of cisplatin used by HIPEC at all dose levels are the best, especially at 100 mg/m^2. The dose recommended by NCCN guidelines in 2020 is 100 mg/m^2. Chinese studies suggest that the maximum dose for patients should be less than 85 mg/m^2.[15,16]

As mentioned above, hyperthermic perfusion can destroy tumour cells and improve drug efficacy, thereby reducing tumour recurrence. Theoretically, normal tissue cells are more resistant to high temperatures than tumour cells and can withstand 60 min at 47℃, while tumour cells can only withstand 60 min at 43℃.[17,18] Additionally, it has been reported that the clinical efficacy of HIPEC is remarkable in adults.[19,20] However, for children, whether hyperthermic perfusion also affects normal cells is a problem worth exploring. Therefore, in the present study, combined with clinical literature and guidelines for the treatment of paediatric nephroblastoma, cisplatin combined with doxorubicin and ifosfamide combined with doxorubicin were used for HIPEC of recurrent nephroblastoma in children. In addition, it was compared with patients receiving no hyperthermic perfusion in the past, so as to observe the clinical efficacy and safety of HIPEC.

This study showed that the total remission rate in the two groups treated with HIPEC was higher than that in the control group. At the 6-month follow-up, no significant differences were found in the recurrence rate between group A and B and the control group, but at the 12-month follow-up, the recurrence rate of group A and B was lower than that of the control group, with statistically significant differences. This indicates that HIPEC can improve the clinical efficacy of patients and reduce recurrence, which is consistent with the results reported in the literature.[21,22] Same as some studies, in this study, the incidence of adverse reactions presented no significant differences during treatment among the three groups, suggesting that HIPEC does not increase the incidence of adverse reactions.[23-25]

Moreover, the short-term safety of HIPEC for recurrent nephroblastoma in children was investigated, revealing that after treatment, the children's vital signs remained stable, and there were no significant changes in WBC count, RBC count or HB. Only the PLA count decreased. The authors analysed the causes and considered that myelosuppression caused by chemotherapeutic drugs was related to the self--loss of tumours, but its specific impact duration and impact on treatment still need to be further determined by clinical observation. In this study, in a short time after treatment, alanine aminotransferase and aspartate aminotransferase in the three groups were significantly higher than those before treatment. However, after liver-protecting therapy, all patients showed no obvious hepatic injury. The cause may be that the high temperature of hyperthermic perfusion leads to ischemic changes in the liver and mild hepatic injury, thus resulting in increased alanine aminotransferase and aspartate aminotransferase in a short time. In future, the observation time still needs to be prolonged to determine the duration of damage to hepatic function. As for renal function, the study found that after HIPEC, creatinine and urea nitrogen increased slightly in a short time and soon returned to the levels before treatment, which may be related to the surgery itself. The specific causes still need further clinical research. However, this study also has some limitations. The study had a small sample size, suboptimal representativeness and some confounding factors. In addition, the observation time of this study is short, and it is not clear whether HIPEC can effectively prolong the survival time of children with recurrent nephroblastoma. The findings still need to be further confirmed by more in-depth studies in the future.

CONCLUSION

In conclusion, the application of HIPEC in the treatment of recurrent nephroblastoma in children has fewer adverse reactions, improves clinical efficacy, reduces the recurrence rate, and has high clinical safety.

ETHICAL APPROVAL:

The study was approved by the Institutional Ethics Committee of Baoding Children's Hospital (No. 2018-02). Written informed consents were obtained from all participants.

PATIENTS' CONSENT:

The author declare that they have obtained from patients informed consent to publish the data concerning this case.

COMPETING INTEREST:

The authors declare that they have no relevant competing interests.

AUTHOR'S CONTRIBUTION:

JW, DM: Designed this study and prepared this manuscript;
YH, NW: Collected and analysed clinical data;
HW, HT: Participated in acquisition, analysis, or interpretation of data and draft the manuscript.
All the authors have approved the final version of the manuscript to be published.

REFERENCES

1. Stokes CL, Stokes WA, Kalapurakal JA, Paulino AC, Cost NG, Cost CR, *et al*. Timing of radiation therapy in pediatric wilms tumour: A report from the national cancer database. *Int J Radiat Oncol Biol Phys* 2018; **101(2)**:453-61. doi:10.1016/j.ijrobp.2018.01.110.
2. Breslow N, Olshan A, Beckwith JB, Green DM. Epidemiology of Wilms tumour. *Med Pediatr Oncol* 1993; **21(3)**:172-181. doi:10.1002/mpo.2950210305.
3. Irtan S, Ehrlich PF, Pritchard-Jones K. Wilms tumour: "State-of-the-art" update, 2016. *Semin Pediatr Surg* 2016; **25(5)**:250-6. doi:10.1053/j.sempedsurg.2016.09.003.
4. Pan C, Cai JY, Xu M, Ye QD, Zhou M, Yin MZ, *et al*. Renal tumour in developing countries: 142 cases from a single institution at Shanghai, China. *World J Pedia* 2015; **11(4)**:326-30. doi:10.1007/s12519-015-0041-3.
5. Group of Urology, Branch of Pediatric Surgery, Chinese medical association. expert consensus on diagnosing and treating wilms' tumour in children. *Chin J Pediatric Surg* 2020; **41(7)**:585-90.
6. Shannon NB, Tan JW, Tan HL. A set of molecular markers predicts chemosensitivity to Mitomycin-C following cytoreductive surgery and hyperthennic intraperitoneal chemotherapy for colorectal peritoneal metastasis. *Sci Rep* 2019; **9(1)**:10572. doi: 10.1038/s41598-019-46819-z.
7. Cravioto-Villanueva A, Cavazos M, Luna-Perez P. Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC) delivered *via* a modified perfusion system for peritoneal carcinomatosis of colorectal origin. *Surg Today* 2016; **46(8)**:979-84. doi: 10.1007/s00595-016-1335-3.
8. Dome JS, Fernandez CV, Mullen EA, Kalapurakal JA, Geller JI, Huff V, *et al*. Children's Oncology Group's 2013 Blueprint for Research:Renal Tumours. *Pediatr Blood Cancer* 2013; **60(6)**:994-1000. doi: 10.1002/pbc.24419.
9. Lopes RI, Lorenzo A. Recent advances in the management of Wilms' tumour. *F1000 Res* 2017; **6**:670. doi: 10.12688/f1000research.10760.1.
10. Hall B, Paussis J, Foster JM. Cytoreduction and hyperthermic intrapeectal peritoneal chemotherapy in the management of colorectal peritoneal metastasis. *Surg Clin North Am* 2017; **97(3)**:671-82. doi: 10.1016/j.suc.2017.01.013.
11. Reutovich MY, Krasko OV, Sukonko OG. Hyperthermic intraperitoneal chemotherapy in serosa-invasive gastric cancer patients. *Eur J Surg Oncol* 2019; **45(12)**:2405-11. doi: 10.1016/j.ejso.2019.07.030.
12. Stevanović S, Draper LM, Langhan MM, Campbell TE, Kwong ML, Wunderlich JR, *et al.* Complete regression of metastatic cervical cancer after treatment with human papillomavirus--targeted tumour-infiltrating T cells. *J Clin Oncol* 2015; **33 (14)**:1543-50. doi:10.1200/JCO.2014.58.9093.
13. Liu L, Zhang N, Min J, Su H, Wang H, Chen D. Retrospective analysis on the safety of 5,759 times of bedside hyperthermic intra-peritoneal or intra-pleural chemotherapy (HIPEC). *Oncotarget* 2016; **7(16)**:21570-8. doi:10.18632/oncotarget.7622.
14. Elawady H, Mahmoud MA, Mostafa DM, Abdelmaksoud A, Safa MW, Elia RZ. Computed tomography virtual cystoscopy for follow-up of patients with superficial bladder tumours in comparison to conventional cystoscopy: An exploratory study. *Arab J Urol* 2016; **14(3)**:192-7. doi:10.1016/j.aju.2016.06.003.
15. Wu L, Lin ZQ. Application of intraperitoneal hyperthermic perfusion chemotherapy in the treatment of advanced ovarian cancer. *J Practical Cancer* 2019; **34(12)**:2086-8. doi:10.3892/ol.2016.4414.
16. Lu HW, Xu MC, Zhang YH. 2021 NCCN ovarian cancer including fallopian tube cancer and primary peritoneal cancer clinical practice guidelines (first edition). *Chinese J Practical Gynecol Obstetrics* 2021; **4(37)**:457-466. doi:10.19538/j.fk2021040113.
17. Long Q, Yang R, Lu W, Zhu W, Zhou J, Zheng C. Adenovirus--mediated truncated Bid overexpression induced by the Cre/LoxP system promotes the cell apoptosis of CD133+ ovarian cancer stem cells. *Oncol Rep* 2017; **37(1)**:155-62. doi:10.3892/or.2016.5263.
18. Kansu-Celik H, Gungor M, Ortac F, Kankaya D, Ensari A. Expression of CD44 variant 6 and its prognostic value in benign and malignant endometrial tissue. *Arch Gynecol Obstet* 2017; **296(2)**:313-8. doi:10.1007/s00404-017-4430-9.
19. Spiliotis J, Nikolaou G, Kopanakis N, Vassiliadou D, Terra A, Efstathiou E. Hepatocellular carcinoma peritoneal metastasis: Role of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC). *Gulf J Oncolog* 2017; **1(24)**:20-3.
20. Yu P, Ye Z, Dai G. Neoadjuvant systemic and hyperthennic intraperitoneal chemotherapy combined with cytoreductive surgery for gastric cancer patients with limited peritoneal metastasis: A prospective cohort study. *BMC Cancer* 2020; **20(1)**:1108. doi: 10.1186/s12885-020-07601-x.
21. Helderman R, Loke DR, Kok SP, Oei AL, Tanis PJ, Crezee J. Variation in clinical application of hyperthermic intraperitoneal chemotherapy: A review. *Cancers* 2019; **11(1)**:78. doi: 10.3390/cancers11010078.
22. Van Driel WJ, Koole SN, Sikorska K, Schagen van Leeuwen JH, Schreuder HWR, *et al*. Hyperthermic intraperitoneal chemotherapy in ovarian cancer. *N Engl J Med* 2018; **378(3)**: 230-40. doi: 10.1056/NEJMoa1708618.
23. Donghyun L, Kim SS, Seong S, Cho W, Yu H. Stage IV wilms tumour treated by korean medicine, hyperthermia and thymosin-α1: A case report. *Case Rep Oncol* 2016; **9(1)**:119-25. doi: 10.1159/000443724.
24. Hayes-Jordan A, Green H, Ludwig J, Anderson P. Toxicity of

hyperthermic intraperitoneal chemotherapy (HIPEC) in paediatric patients with sarcomatosis/carcinomatosis: Early experience and phase 1 results. *Paediatr Blood Cancer* 2012; **59(2)**:395-7. doi: 10.1002/pbc.24160.

25. Weatherall AD, Bennett TR, Lovell M, Fung W, de Lima J. Staged intraperitoneal brachytherapy and hyperthermic intraperitoneal chemotherapy in an adolescent: Novel anesthetic challenges for pediatric anesthetists. *Paediatr Anaesth* 2017; **27(4)**:338-45. doi: 10.1111/pan.13094.