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Comparative study of quality of life, adverse effects after cytoreduction and HIPEC in stage IIIA-IIIC ovarian cancer

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Abstract

Nowadays cytorective surgery and HIPEC is the mainstay of management of advanced stages ovarian cancer. Study was conducted to assess the effectiveness of combined treatment in IIIA-IIIC ovarian cancer, its impact on quality of life. 37 patients of main group (CRS + HIPEC) were compared with 25 patients of control group (surgery + systemic chemotherapy). The quality of life was assessed with Medical Outcomes Study 36-Item Short Form Health Survey (SF-36). Comparative analysis of quality of life 6 months after treatment completion did not show significant statistical difference. Combination of cytoreduction with HIPEC improves quality of life in patients with ovarian cancer, is tolerated better and has less systemic toxicities than systemic chemotherapy.

Key words: ovarian cancer, treatment, HIPEC, cytoreduction, chemotherapy.

Actuality. Ovarian cancer remains a complicated medical issue. According to worldwide statistics, 1-year, 3-year and 5-year survival rates are 63%, 41%, 35% respectively. In the last decade a modest decrease of 5-year survival was caused by more common use of platinum-based chemotherapy for disseminated ovarian cancer [1].

More than 70% cases of ovarian cancer are revealed at late stages, that accounts for poor prognosis. Contemporary treatment standards include combination of surgical cytoreduction and platinum-based chemotherapy. However, even after complete cytoreduction with adjuvant first-line systemic treatment, that achieved complete clinical regression, 5-year survival rates for III and IV stages are 20% and 10% respectively [2].

Most patients respond well to first-line therapy, although 30% may have a platinum-resistant or platinum-refractory tumors. In such cases other cytostatic drug combinations, target therapy and immunotherapy is recommended [3]. To sum up, despite absence of clinical signs, one third of patients after first-line chemotherapy will have relapse in 2-3 years. Objective response rate is 10-25%, median survival time is 7-18 months [4]. Most studies share an opinion, that optimal cytoreduction is crucial for effective treatment. However, only 10-15% of performed surgeries achieve optimal extent. That's why it is still relevant to improve methods of surgical and adjuvant methods of ovarian cancer treatment [5].

Study was conducted to assess the effectiveness of cytoreductive surgery in combination with hyperthermic intraperitoneal chemoperfusion (HIPEC) in advanced stages ovarian cancer management. We present the experience of University clinic of Odessa National Medical University.

Materials and methods. We've analyzed 37 cases of ovarian cancer treated with cytoreduction, HIPEC and 4-6 courses of adjuvant chemotherapy. Study has been conducted in the Department of Surgery №4 with the Course of Oncology (Odessa National Medical University) since 2015. All patients had serosal papillary ovarian cancer FIGO IIIA-IIIC. Patients age was 21-59 years. Control group included 25 patients after surgical treatment and convenient systemic chemotherapy. All patients received suboptimal cytoreduction.

Criteria of exclusion were age more than 70 years, extensive canceromatosis with peritoneal canceromatosis index more than 20, unresectable small bowel involvement, distant metastasis, retroperitoneal lymphadenopathy, unresectable retroperitoneum invasion, severe concomitant pathology. Previous surgeries with massive adhesions were considered as relative contraindication.

Cytoreduction included visceral resections and peritonectomy. We performed hysterectomy with bilateral adnexectomy, omentectomy and selective parietal peritonectomy.

In our institution we perform HIPEC with Performer LRT (Rand, Italy). Its main components are two pumps, heater, infusion lines and digital integrational system. The apparatus controls the procedure automatically and allows fine tuning and monitoring of different parameters like temperature, volume speed, target volumes and timing.

All patients in the main group received HIPEC with cisplatine and doxorubicine. Drugs are dissolved in 5000-6000 ml of isotonic perfusate. We use a closed technique, that is after wound closure 5-6 silicone drains are placed into abdominal and pelvic cavity. Procedures lasted 60-90 minutes with target intraperitoneal temperature 40-41^{o}C and volume speed 800-900 ml/min. Mean filling volume is 2500-3000 ml depending of patients constitution. The washout phase takes 10-15 minutes until clear outflow and normothermia is achieved.

All patients received cytoprotection with thiosulfate during HIPEC and 6 hours -after to prevent systemic toxicity of cisplatine. Usually patients stayed for one day in the intensive care unit. Perioperative medications include dexamethasone, 5-HT blockers, adequate analgesics and infusional therapy. Antibiotic prophylaxis s protracted for 1-3 days if needed.

Patients were assessed intraoperatively according to peritoneal canceromatosis index, previous surgical score, cytoreduction completeness score. The quality of life was analyzed with Medical Outcomes Study 36-Item Short Form Health Survey (SF-36). Adverse effects and toxicities were secondary outcomes of the study.

Results. Among the main group (n=37) IIIA, IIIB, IIIC stages were revealed in 5, 3 and 29 patients respectively. In the control group (n=25), 10 patients had IIIA, 2 patients – IIIB, 13 patients – IIIC. Canceromatosis index in the main group was LS-1 (28,0%) and LS-2 (72,0%). It didn`t differ significantly in control group: LS-1 - 36,0%, LS-2 – 64,0%. Cytoreduction completeness score had no statistical difference (CC-1 and CC-2 was 28,0%, 72,0% in main group, 36,0%, 64,0% in control group).

Comparative analysis of quality of life 6 months after treatment completion didn’t showed nonsignificant statistical difference (table 1).

Table 1. Comparison of the Short Form (36) Health Survey

SF-36 Scale	**Main group (n=37)**	**Control group (n=25)**
Physical activity	34,08±21,14	31,88±19,44
Physical role functioning	28,42±13,43	21,01±14,23
Bodily pain	46,29±16,23	41,27±20,11
General health perceptions	35,33±14,76	33,72±23,27
Vitality	49,85±24,16	44,25±34,26
Social role functioning	65,42±26,16	63,12±22,39
Emotional role functioning	42,11±15,46	44,25±17,24
Mental health	66,32±22,26	59,32±22,26

No allergic and idiosyncratic drug reactions were observed in the main group. 9 patients had temporary hyperthermic reaction, controlled with NSAIDs.

Few patients (n=5, 13,5%) complained about pain around drain contrapertures.

Toxicities comparison of treatment regimens is shown in the Table 2, 3.

Table 2. Adverse effects of treatment in the main group

Toxicity	Toxicity grade				Overall, %
	I, n (%)	II, n (%)	III, n (%)	IV, n (%)	
Leukopenia	13 (35,1)	7 (18,8)	4 (10,8)	3 (8,1)	72,8
Neutropenia	12 (32,4)	6 (16,2)	5 (13,5)	–	62,1
Anemia	3 (8,1)	2 (5,4)	–	–	13,5
Thrombocytopenia	6 (16,2)	–	–	–	16,2
Nausea	7 (18,9)	5 (13,5)	5 (13,5)	–	45,9
Vomiting	16 (43,2)	1 (2,7)	1 (2,7)	–	48,6
Diarrhea	3 (8,1)	–	–	–	8,1
Stomatitis	8 (21,6)	1 (2,7)	–	–	24,3

Table 3. Adverse effects of treatment in the control group

Toxicitys	Toxicity grade				Overall, %
	I, n (%)	II, n (%)	III, n (%)	IV, n (%)	
Leukopenia	10 (40,0)	8 (32,0)	1 (4,0)	1 (4,0)	80,0
Neutropenia	11 (44,0)	4 (16,0)	2 (8,0)	1 (4,0)	72,0
Anemia	5 (20,0)	4 (16,0)	4 (16,0)	–	52,0
Thrombocytopenia	4 (16,0)	–	–	–	8,0
Nausea	7 (28,0)	4 (16,0)	4 (16,0)	–	60,0
Vomiting	10 (40,0)	4 (16,0)	1 (4,0)	–	60,0
Diarrhea	3 (12,0)	–	–	–	12,0
Stomatitis	2 (8,0)	4 (16,0)	1 (4,0)	–	28,0

Hematological, gastrointestinal adverse effects were comparable in both groups. Less nephrotoxicity was observed in the control group.

Mean hospital stay was 8,9 days in the main group and did not differ significantly from control group.

Discussion. Cytoreduction and HIPEC have a reasonable rationale. Several tumors (ovarian cancer, malignant mesothelioma, colorectal and gastric cancer), that evolve into peritoneal carcinomatosis, in some stages of development are locally contained within serosal lining without giving distant metastases [6]. Macroscopic tumor removal with surgical cytoreduction and microscopic with HIPEC achieves locoregional control.

By definition, chemotherapeutic drugs have various grades of systemic toxicities. Their use in high concentrations may cause serious adverse effects. Regional chemotherapy

can achieve high local concentrations without systemic leakage into systemic circulation. Hyperthermia has direct selective cytotoxicity and acts synergistically with alkylating agents, like anthracyclines [7]. In addition, it improves drug penetration into tumor deposits. Continuous cavity chemoperfusion supports constant chemotherapeutic agents concentration and equal distribution. These features explain better "local" intraperitoneal control after HIPEC comparing to systemic chemotherapy.

Conclusions

1. Combination of cytoreduction with HIPEC improves quality of life in patients with ovarian cancer.

2. HIPEC is proven to be effective in conjuction with optimal or suboptimal cytoreduction.

3. HIPEC is tolerated better and has less systemic toxicities in comparison with systemic chemotherapy.

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