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Response to Second Line Chemotherapy in Ovarian Cancer of Epithelial Origin

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Abstract—*Among 45 patients with stage II, III and IV ovarian cancer of epithelial origin, a good response to second line chemotherapy (SLC) was observed in 7 (15.6%). No correlation was found between the response rate and histological category. No statistically significant correlation was found between response to primary chemotherapy and SLC. A better response to SLC was observed in state II patients and in patients in stage III and IV who underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy compared to those who underwent a less extensive procedure. The survival of responders to SLC was significantly higher than that of non-responders.*

INTRODUCTION

OVARIAN cancer is the most common gynecological malignancy in Israel. Similar to other Western countries, most tumours are of epithelial origin and the majority of the patients have advanced disease at the time of diagnosis[1]. Chemotherapy is an important component in the post-operative treatment of these patients. Since a considerable proportion of the patients do not respond to primary chemotherapy, or the response is only temporary, second line chemotherapy (SLC) is often used [2–8].

The purpose of the present retrospective study was to evaluate the response rate to SLC.

MATERIALS AND METHODS

During the 7-year period 1970–1976, 67 patients with histologically confirmed ovarian carcinoma of epithelial origin received post-operative chemotherapy at the Chaim Sheba Medical Center, Tel-Hashomer. Of these 67 patients, 45 received SLC because they either failed to respond to the initial treatment or developed resistance after a period of response, and they comprise the study group. The age of these patients ranged from 19 to 72, with a mean of 54.5 yr. Staging was done during exploratory laparotomy according to FIGO. Nine patients were in stage II, 24 in stage III and 12 in stage IV. Total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH + BSO) was performed in 8 of 9 patients with stage II, in 5 of 24 with stage III and in 4 of 12 in stage IV. None of the patients who received SLC were in stage I at the time of diagnosis. All of them had at least two courses of primary chemotherapy and two of SLC, and survived a minimum of one month after initiation of SLC. Forty-one of them received radiotherapy by the "moving strip and pelvic boost" technique prior to primary chemotherapy.

Chemotherapy was not uniform, each chemotherapist using his drugs of choice. During primary chemotherapy 39 (86.7%) patients were treated with an alkylating agent alone (cytoxan—11 patients; thiotepa—9 patients), or with an alkylating agent combined with an antimetabolite (thiotepa with methotrexate—19 patients). The rest received other agents. During SLC 19 (42.2%) were treated with single drugs (6 with cytoxan, 4 with melfalan, 6 with 5-fluorouracil and 3 with other agents) and 26 (57.8%) with combined chemotherapy (14 with methotrexate and thiotepa, 6 with melfalan and 5-fluorouracil, 3 with cytoxan and 5-fluorouracil, and 3 each with other combined chemotherapy). The most common drugs used and dose schedules are listed in Table 1.

Patients were considered to have a good response to chemotherapy when tumour masses decreased in size by 50%, when ascites subsided or when symptoms were alleviated for three months or more. Patients with static or progressing disease were considered as having

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Table 1. Chemotherapeutic agents used during primary and second line chemotherapy

Drug	Dose
Thiotepa	10 mg/day i.v. × 5–7 days, and after a 2-week interval 15 mg i.v. weekly
Cytoxan (CTX)	Loading dose—2–6 mg/kg/day for 4–10 days, then a maintenance dose of 1–3 mg/kg orally
Melphalan (MEL)	0.2 mg/kg/day orally × 5 days; repeated every 4 weeks
5-Fluorouracil (5FU)	15 mg/kg/day i.v. × 5–10 days, then weekly 10 mg/kg i.v.
Methotrexate (MTX)	5–7.5 mg/day orally × 3–4 days; repeated every 2–3 weeks
Thiotepa + MTX	Thiotepa 15 mg/day i.m. × 5 days; MTX 7.5–10 mg/day orally till toxicity
MEL + 5 FU	MEL 0.2 mg/kg/day orally × 5.5 FU 8 mg/kg/day i.v. × 5; Repeated every 3–4 weeks
CTX + 5 FU	CTX 7 mg/kg/day i.v. × 5.5 FU 8 mg/kg/day i.v. × 5; Repeated every 3–4 weeks.

no response to chemotherapy. Survival was estimated by the actuarial life table analysis and comparison of survival by the log-rank methods [9].

RESULTS

Among the 45 patients who received SLC a good response was observed in 7 (15.6%) patients.

Table 2 presents the response of these patients to primary chemotherapy and SLC according to the type of chemotherapy used. The overall pattern of response was similar during primary chemotherapy and SLC for single agent and combined chemotherapy. However, the patients who responded well to primary treatment were not necessarily those who responded well to secondary therapy, as detailed below.

Table 3 presents the response rate to primary chemotherapy and SLC according to the type of operation performed, the clinical stage at the time of diagnosis, the histological category and administration of radiotherapy. The response rate to SLC was significantly higher [P(Fisher's exact test for 2×2 tables) = 0.02] in patients who underwent TAH + BSO than in patients who underwent less extensive procedures. The same trend was observed with respect to primary chemotherapy, although it did not reach significance [P(Fisher's exact test for 2×2 tables) = 0.10]. There was a significantly better response rate [P(Fisher's exact test for 2×2 tables) = 0.01] to SLC of patients in stage II than that of patients in stage III and IV, while the response rate to primary chemotherapy was similar in all stages. Since in stage II all but one patient underwent TAH + BSO while in stages III and IV only 25% underwent this procedure, the combined effect of both factors was analyzed. A better response rate to SLC of borderline significance [P(Fisher's exact test for 2×2 tables) = 0.057] was noted in stages III and IV patients who underwent TAH + BSO. No correlation was evident between the response rate and histological category of the tumour or the administration of radiotherapy prior to chemotherapy.

Table 4 presents the response rate to SLC according to the type of response to primary chemotherapy. There was a higher response to SLC in patients who had a good response to primary chemotherapy as compared to patients who did not respond to primary chemotherapy (33.3% vs. 11.1%). The difference was not, however, statistically significant [$P(\chi^2) > 0.3$].

*Table 2. Response to primary and second-line chemotherapy by type of agents used**

	Chemotherapy					
	Primary			Second-line		
		Good response			Good response	
	Total	No.	%	Total	No.	%
Single agent—total	25	7	28.8	19	3	15.6
Alkylating agent	20	7	35.0	10	2	20.0
Antimetabolite	5	0	0.0	6	0	0.0
Other	—	—	—	3	1	33.3
Combined—total	25	3	15.0	26	4	15.4
Alkylating agent + antimetabolite	19	3	15.8	23	3	13.0
Other	1	0	0.0	3	1	33.3

*Analysis was done separately for primary and for second-line chemotherapy. Thus the 19 patients who received single agent second-line therapy are not necessarily among the 25 who received single agent primary chemotherapy, etc.

Table 3. Response rate to primary and secondary chemotherapy according to surgical procedures, clinical stage at diagnosis, histological category and administration of radiotherapy

	Total	Good response to chemotherapy			
		Primary		Secondary	
	No.	No.	%	No.	%
Surgical procedure					
TAH + BSO	17	6	35.2	7	41.2
Less extensive procedure	28	4	16.6	0	0.0
Stage					
II	9	2	22.2	5	55.5
III	24	5	20.8	1	4.2
IV	12	3	25.0	1	8.3
Stage and surgical procedure					
II with TAH + BSO	8	2	25.0	4	50.0
II without TAH + BSO	1	0	0.0	0	0.0
III and IV with TAH + BSO	9	3	33.3	2	22.2
III and IV without TAH + BSO	27	3	11.1	0	0.0
Histology					
Solid adenocarcinoma	27	8	29.6	4	14.8
Serous cystadenocarcinoma	11	2	18.2	1	9.1
Mucinous cystadenocarcinoma	7	0	0.0	2	22.2
Radiotherapy					
Given	41	9	21.1	6	14.6
Not given	4	1	25.0	1	25.0

Table 4. Response to second-line chemotherapy according to type of response to primary chemotherapy

Primary chemotherapy	No.	Second line chemotherapy		
			No.	%
Good response	10	Good response	3	33.3
		No response	7	67.7
No response	35	Good response	4	11.4
		No response	31	88.6

Table 5. Survival of patients according to response to second line chemotherapy

	Survival	
	3 years	5 years
Good response	71.4%	53.6%
No response	10.5%	0.0%

Table 5 presents the 3- and 5-year survivals of the patients according to the type of response to SLC. The survival of patients with a good response to SLC was significantly [$P(\chi^2) < 0.001$] higher in patients with a good response than in patients with no response to SLC.

DISCUSSION

The overall response rate to SLC in this retrospective series was 15.6% and is in the range of the rate reported in other series employing similar chemotherapeutic agents [3–8]. These patients also had a significantly better survival. No significant differences in response rate among the different histological categories of ovarian epithelial tumours were observed. The majority of neoplasms were, however, reported as adenocarcinoma without further specification, in contrast to most other series of epithelial tumours, in which the most common neoplasm is serous cystadenocarcinoma [1, 3]. It has been suggested that radiotherapy decreases the response rate to subsequent chemotherapy [10]. The small number of patients who did not receive radiotherapy in our series precludes evaluation of this effect.

Two factors seemed to have influenced the response rate to SLC. Patients in the earlier stages at diagnosis had a better response rate. Also, a better response was observed in stage III and IV patients who underwent TAH + BSO than in patients who underwent less extensive procedures. While all patients but one in stage II underwent TAH + BSO, only 9 out of the 36 patients in stages III and IV underwent this procedure as "debulking" of tumours was not yet customary during the study period. The trend for better response to

SLC of stage III and IV patients who underwent TAH + BSO is in line with the current concept of the value of maximal tumour mass reduction at the initial operation [4, 11, 12].

The clinician facing lack of response to primary chemotherapy often asks himself whether subjecting the patient to SLC and its possible complications is justified. Our data, while based on treatment schedules currently used infrequently for ovarian cancer, seem to indicate that there is a group of patients who respond well to SLC in spite of lack of response to primary chemotherapy.

It may be expected that with the current aggressive surgical approach and subsequent treatment with new chemotherapeutic agents and treatment schedules [13, 14] better results will be obtained.

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