Can Integrative Oncology Increase Adherence to Chemotherapy in Advanced Gynecologic Cancer?

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Abstract

Objective

Integrative oncology (IO) has been shown to improve quality-of-life (QoL) and increase adherence to planned chemotherapy regimens. This study examined the impact of a patient-tailored IO program on adherence to chemotherapy among patients with advanced gynecological cancer.

Methods

This prospective pragmatic study examined patients with stage III/IV gynecological cancers undergoing 6 weeks of weekly IO treatments. Adherence to the planned chemotherapy regimen was assessed using the relative dose intensity (RDI) calculation. Patients consistently attending IO treatments (consistent-IO group) were compared to those who were not (non-consistent IO group).

Results

RDI was calculated for 73 patients in the consistent-IO group (99 chemotherapy cycles) and 61 in the non-consistent-IO group (96 cycles with IO care, 126 cycles without). Both groups had similar baseline demographic characteristics, with endometrial cancer more prevalent in the consistent-IO group. RDI was significantly less reduced in the consistent-IO chemotherapy group ($p = 0.005$). During taxane-based regimens RDI was better maintained in the consistent-IO group (0.93 vs. 0.87, $p = 0.012$), though not with platinum-based cycles. Linear regression model found a correlation between preserved RDI and consistent attendance at weekly IO treatments, and lower rates of chemotherapy-induced peripheral neuropathy and pain.

Conclusion

Patient-tailored IO programs for patients with advanced gynecological cancer may help preserve adherence to chemotherapy at 6 weeks, especially with taxane-based regimens. Further research needs to explore whether this correlation is chemotherapy agent-specific.

1. Introduction

The term "Integrative Oncology" (IO) describes a framework in which complementary medicine practices are provided to patients within conventional oncology settings. IO services are becoming increasingly evident in many of today's oncology centers, with the stated goal “to optimize health, quality of life, and clinical outcomes across the cancer care continuum”. The emphasis on a patient-centered and patient-tailored treatment approach is core to these IO services, and focuses primarily on improving patients' quality of life (QoL) and wellbeing. There is a large body of research examining the impact of IO on QoL-

related concerns, particularly in the treatment of patients with breast and gynecological cancer. This research has shown significantly beneficial effects of these therapies in the relief of cancer-related fatigue, pain, appetite, nausea/vomiting and sleep-related disturbances, more so among patients who are consistent (i.e., adherent) in their attendance of patient-tailored IO programs[19].

Clinical research has also demonstrated a statistically significant correlation between consistent attendance at IO treatment programs and patient adherence to their conventional oncology regimen, as measured using the relative dose intensity (RDI) of chemotherapy. A greater preservation of RDI scores (i.e., greater adherence) was found among patients undergoing chemotherapy for breast and gynecological cancer who were consistent in their attendance at weekly IO sessions. In patients with advanced gynecological cancers, an association was suggested between consistent attendance at IO treatments and higher 3-year survival rates, though RDI was not calculated in this study. The findings of this research, however, have been methodologically limited by its pragmatic, non-randomized methodology, with the incorporation of patient preference and heterogeneity of the individually-tailored IO treatments.

The present study examined as its primary outcome the impact of a patient-tailored IO treatment program on the adherence of patients with advanced gynecological cancers to their planned chemotherapy regimen.

2. Methods

2.1 Study design and setting

The study was conducted within a prospective, patient-preference, non-randomized pragmatic study with the primary goal of examining the effect of a patient-tailored IO program on patient adherence to their planned chemotherapy regimen. The primary study outcome, RDI, was calculated based on chemotherapy dosage and cycle interval documented in the prospective study for patients with advanced gynecological cancer (ovarian, endometrial, cervical) who were undergoing cycles of chemotherapy over a 6-week study period. The study took place at the Oncology Service of Clalit Healthcare Services at the Lin and Zebulon Medical Centers, Haifa, Israel. The Oncology Services at these centers provide patients undergoing chemotherapy and/or palliative care with IO modalities, administered by a multidisciplinary team of practitioners (physicians, nurses, from conventional medical, paramedical and non-medical fields), all trained in integrative and supportive oncology care. Study recruitment took place between July 2009 to November 2020.

2.2 Study population and inclusion/exclusion criteria

Eligible patients were aged ≥ 18 years and diagnosed with stage III-IV gynecological cancer who were undergoing chemotherapy for at least 6 weeks. All patients were made aware of the option to receive IO treatments in parallel to their conventional care, throughout the study period. Patients whose IO treatments took place either before or after chemotherapy, or for whom no palliative chemotherapy

regimen was planned, were excluded from the study eligibility. Patients scheduled for chemotherapy during the 6-week study period, but for whom it was either not administered or curtailed, were excluded as well.

2.3 Patient-tailored IO treatment program

Patients were referred to the initial integrative physician (IP) consultation by one of their healthcare professionals (HCPs). These included oncologists, oncology gynecologists, nurse-oncologists and psycho-oncologists). The IP is a licensed medical doctor with dual training in supportive cancer care and complementary medicine. The IP consultation is conducted as a structured interview that includes standardized QoL-focused questions and assessment tools, aimed at co-designing (with the patient and the referring HCP) a comprehensive, patient-centered and tailored weekly IO treatment program, for a period of at least 6 weeks. The IO treatment plan includes the following themes: * addressing the patient's expectations and health-belief model * identifying the severity of their concerns and wellbeing, for both general and specific QoL-related symptoms and chemotherapy-related toxicities * anticipating expected toxicities of the planned chemotherapy regimen and probable need to reduce (or discontinue) dosing as a result of these adverse effects * assessing the findings of the research regarding the effectiveness and safety of the planned IO treatments * addressing the indications listed in the HCP referral, with the HCP's input provided throughout the study period.

Assessment of QOL-related concerns was conducted using the following validated questionnaires: ESAS, Edmonton Symptom Assessment Scale; and EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire ".

2.4 Patient-tailored IO treatment program

The IP-patient-HCP co-designed IO treatment program entails weekly IO treatments provide by a multi-disciplinary team of IO practitioners, including physicians, nurses, para-medical and complementary medicine healthcare providers, all trained in integrative oncology. The training program ensures that IO practitioners maintain a standardized patient-tailored approach, emphasizing the following elements: Re-assessment of treatment goals and re-modeling the treatment plan, according to the patient's expectation and QoL-related concerns; implementation of IO-related guidelines for clinical practice to enhance treatment effectiveness and safety; and ensuring weekly continuity of care, in which the same IO practitioner is assigned as a case manager and responsible for coordinating treatments with other IO practitioners in cases where accessibility is limited.

Weekly IO treatments last between 30–45 minutes and include one or more of the following IO modalities: guidance on the use of herbal and dietary supplements; acupuncture and other manual and movement modalities (e.g., Anthroposophic medicine, acupressure, reflexology, Feldenkrais and Paula methods aimed at alleviation of pain and improved gastro-intestinal functioning); and mind-body-spirit therapies (e.g., guided imagery, spiritual care). Attendance of the IO program is considered consistent when the patient attends at least 5 treatment sessions (≤ 30 days between each session) during the 6-week period following the IP consultation.

The IP consultation and subsequent IO treatments are provided free-of-charge for all patients. Throughout the study period all patients receive standard conventional palliative/supportive care, which included consultations and medications, including analgesics; nurse-provided care; and psycho-oncology interventions.

2.5 Study groups

Patients were allocated to one of two study groups, based on their attendance at the IO treatment sessions during the 6-week study period (Fig. 1):

1. Consistent IO group (Group 1): patients who were consistent in their attendance of IO treatment sessions throughout their entire gynecological oncology chemotherapy cycles, including during the 6-week study period.
2. Non-Consistent IO group (Group 2): patients who, throughout their gynecological oncology treatment, attended concomitant IO treatment sessions during only some of the chemotherapy cycles. This group was further divided to two subgroups according to the number of cycles with or without concomitant IO treatment: Group 2.1, chemotherapy cycles accompanied by IO treatment sessions during the 6-week study period; and Group 2.2., chemotherapy cycles with no IO treatment sessions provided during the 6-week study period

2.6 Adherence to chemotherapy

Chemotherapy regimens scheduled to be administered during the 6-week study period were considered eligible for assessment of adherence (RDI). These included regimens in which chemotherapy agents were administered once weekly, every two weeks, or every 3 weeks, all for a minimum period of 6 weeks.

The primary study outcome was patient RDI, which included the planned dosing for each chemotherapy agent, calculated using the standard published recommended dosages for each regimen. The planned dose was then compared with the actual dose administered to the patient, based on the oncology nurse computerized patient file. RDI was calculated as the ratio of the drug dose administered (mg)/treatment time interval (weeks) divided by the planned dose (mg)/treatment time interval (weeks).

An RDI value of 1.0 indicates that the planned chemotherapy regimen was implemented in its entirety, with respect to both dosing and timing of the treatment schedule. In the present study, we considered an RDI $\geq$ 0.97 as reflecting complete adherence, this in order to account for instances in which chemotherapy was delayed for 24 hours because of logistical factors, and not those related to the patient's medical condition. For multi-agent regimens, the RDI was calculated separately for each agent, with a mean total RDI then calculated for the entire regimen. RDI was calculated from day 1 of the chemotherapy cycle for the entire 6-week period, when administered as planned; or until completion of the planned chemotherapy cycle, if a delay resulted from patient-related causes (e.g., deteriorating health) or severe chemotherapy-related toxicities. When IO treatments were provided concomitantly with

chemotherapy, RDI was calculated from Day 1 of that cycle. When IO treatments were not provided concurrently with chemotherapy, the first chemotherapy cycle (Cycle 1-Day 1) was used to calculate RDI.

The percentage of patients with a reduced RDI (i.e., < 0.97) was determined by calculating the percentage of patients in each arm of the study for whom the dose intensity of the chemotherapy regimen was reduced from that which was planned, for either the total dosage of the agents being given (in mg) or the frequency of the administered treatment schedule (in weeks). RDI was also calculated separately for those chemotherapy regimens based on taxane and platinum-based agents.

2.7 Data analysis

The study sample size was calculated using the OpenEpi program (Microsoft). It was determined that at least 60 patients would need to be included in each arm to assess the impact of IO on the primary study RDI outcomes. This would allow an alpha-error of 0.05 and beta-error of 0.2 (power 80%) to detect a difference of 20% difference in RDI ranging in a 0–1 scale. Data were collated and entered into an SPSS software program (version 27; SPSS Inc., Chicago, IL). Pearson's chi-square test and Fisher's exact test were used to detect differences in the prevalence of categorical variables and demographic data between participants in both groups. A t-test was performed to determine differences in continuous variables when normality was assumed. Where distribution was abnormal a Mann-Whitney U test was used. P values of < 0.05 were regarded as statistically significant. A linear regression model was used to predict total RDI in chemotherapy cycles, whether IO treatments were or were not administered. Following preliminary analysis of chemotherapy cycles-related variables, the model predicted RDI independently from the following variables: age, study group consistency (consistent or non-consistent groups), with respect to integrative care (consistent vs. non-consistent); and chemotherapy-induced peripheral neuropathy (report or no-report of pain and/or neuropathy symptoms).

2.8 Ethical Considerations

Participation in the study was voluntary, without payment or other incentive offered to participants. Study participation was clearly and openly offered to patients of any ethnic origin or religion. The protocol of the study was approved by the Ethics Review Board (Helsinki Committee) of the Carmel Medical Center in Haifa, Israel; and was registered at ClinicalTrials.gov (NCT01860365).

3. Results

3.1 Characteristics of Study Groups

A total of 350 files of patients undergoing chemotherapy for advanced gynecological cancer during the study period were examined. Of these, 151 were of patients who had been referred to the initial IP, with 134 of those attending the consultation considered eligible for study participation: 73 (54.5%) in the consistent IO group (Group 1), and 61 in the non-consistent IO group (Group 2; Fig. 1).

The demographic, cancer and oncology treatment-related characteristics of the two groups are presented in Table 1. Patients in both groups had similar baseline demographic parameters; frequency of reported complementary medicine use; attitudes regarding the effectiveness and risks associated with these practices; and a belief in the existence of a connection between body and soul, and their relatedness to spiritual elements. In contrast, the two groups varied in their oncological parameters, with those in the non-consistent IO group having a greater frequency of ovarian carcinoma (P = 0.005), lower rates of endometrial cancer (P = 0.013), and higher prevalence of metastatic disease (P = 0.035). Patients in the two groups were similar in the characteristics of the HCPs who referred them to the IP consultation, as well as in their overall EORTC QOL-related outcomes at baseline. In both study groups, a patient-tailored multi-modal (in which ≥ 1 IO modalities were used concurrently) treatment was provided to more than 90% of patients (Fig. 2) with acupuncture (used by 57.5% and 60.7% of patients in the consistent and non-consistent groups), manual-movement, and herbal medicine modalities being the ones most frequently used.

Table 1
Characteristics of patients in consistent (Group 1) or non-consistent with IO care (Group 2; see text; data from the initial IP consultation)

	Consistent IO group **n = 73**	**Non-consistent IO group**[Ω] **n = 61**	***P* values**
Mean Age ± SD	63.2 ± 9.9	62.9 ± 10.0	P = 0.87
Primary Language Hebrew	60 (82%)	43 (70.5%)	P = 0.15
Country of Birth Israeli-born	36 (53%)	32 (54%)	P = 1.00
Residence Haifa & suburbs	50 (68.5%)	43 (70.5%)	P = 0.85
Education High school & academic	41 (91%)	40 (91%)	P = 1.00
Occupation Unemployed	9 (21%)	8 (18%)	P = 0.79
Income ≤ Average	31 (70.5%)	35 (76%)	P = 0.64
Stated Religion Jewish	38 (86%)	39 (85%)	P = 1.00
Level of Religiosity Secular	32 (71%)	33 (70%)	P = 1.00

AIC, Adherence to Integrative Care; CM, complementary medicine

Ω **The non-consistent IO group (**Table 1**) refers to the 2.1 and 2.2 groups mentioned in** Table 2

≠ Percentages are presented concerning the number of respondents to each of the demographic items

* Data based on a Likert scale scored from 1 (very slightly agree) to 7 (agree very much)

***HCP, healthcare professional

¥ Data based on question 30 in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30); scores range from 1 (not at all) to 4 (very much).

	Consistent IO group n = 73	Non-consistent IO group[Ω] n = 61	*P* values
Familial status Married	27 (61%)	31 (66%)	P = 0.67
Informal Caregiver Spouse	28 (67%)	28 (67%)	P = 1.00
Primary Cancer site: Ovarian Endometrial Cervical	37 (51%) 31 (43%) 5 (6%)	49 (80%) 10 (16%) 2 (3%)	P = 0.005 P = 0.013 P = 0.45
Evidence of metastasis Yes	25 (36%)	33 (55%)	P = 0.035
Prior CM use Non-cancer related: Yes	46 (63%)	38 (62%)	P = 1.00
Cancer-related CM use Yes	41 (56%)	33 (54%)	P = 0.86
CM perceived as effective* mean ± SD	6.07 ± 1.19	5.66 ± 1.29	P = 0.21
CM perceived as risky* mean ± SD	1.72 ± 1.78	1.13 ± 0.43	P = 0.085

AIC, Adherence to Integrative Care; CM, complementary medicine

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¥ Data based on question 30 in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30); scores range from 1 (not at all) to 4 (very much).

	Consistent IO group n = 73	Non-consistent IO group[Ω] n = 61	*P* values
Is there a connection between body and **soul?*** mean ± SD	6.22 ± 1.61	6.08 ± 1.21	p = 0.67
Relatedness to spiritual contents* mean ± SD	4.68 ± 2.28	4.31 ± 2.15	P = 0.46
Referring HCP**: Oncologist/surgeon Nurse oncologist Psycho-oncologist	20 (44%) 22 (49%) 3 (7%)	18 (39%) 24 (52%) 4 (9%)	P = 0.85
EORTC Self-assessed quality of life[¥] mean ± SD	3.30 ± 1.39	3.04 ± 1.39	P = 0.38
ESAS fatigue mean ± SD	5.70 ± 2.78	6.65 ± 2.65	P = 0.095
ESAS anxiety mean ± SD	4.32 ± 3.43	4.07 ± 3.55	P = 0.73
AIC, Adherence to Integrative Care; CM, complementary medicine			
[Ω] **The non-consistent IO group (**Table 1**) refers to the 2.1 and 2.2 groups mentioned in** Table 2			
[≠] Percentages are presented concerning the number of respondents to each of the demographic items			
* Data based on a Likert scale scored from 1 (very slightly agree) to 7 (agree very much)			
***HCP, healthcare professional			
[¥] Data based on question 30 in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30); scores range from 1 (not at all) to 4 (very much).			

3.2 Adherence (RDI)-related outcomes

Table 2 and Fig. 1 present the findings regarding the adherence (i.e., RDI) of both study groups to their chemotherapy regimen. Figure 1 also presents the factors which resulted in exclusion from the study analysis. The consistent IO group (Group 1; 73 patients) received a total of 102 chemotherapy cycles during the 6-week study period, during which they were treated concomitantly with IO modalities and for which 99 **cycles** were analyzed. The non-consistent IO group (Group 2; 61 patients) underwent 255 chemotherapy cycles, of which 222 were analyzed as a whole and as two subgroups: Group 2.1, in which

96 chemotherapy cycles were given along with IO treatments; and Group 2.2, with 126 chemotherapy cycles without any IO treatments provided at the same time.

Table 2
RDI-related outcomes for chemotherapy cycles in patients consistent (Group 1) or non-consistent with IO care (Group 2)

Characteristic	**Group 1** **Chemo cycles in the consistent group** **n = 99**	**Chemo cycles in the non-consistent group n = 222**			***P* values**
		Group 2 **Entire cycles** **n = 222**	**Group 2.1** **Cycles with IO** **n = 96**	**Group 2.2** **Cycles with no IO** **n = 126**	
Age during the cycle mean ± SD	63.8 ± 9.1	63.5 ± 11.7	63.15 ± 11.9	63.8 ± 11.7	P = 0.88
Chemotherapy type (% of cycles) Taxanes	64 (65%)	93 (42%)	50 (52%)	43 (34%)	P^1 < 0.001 P^2 = 0.009 P^3 = 0.08 P^4 < 0.0001
Platins	84 (85%)	118 (53%)	65 (78%)	53 (42%)	P^1 < 0.001 P^2 = 0.002 P^3 = 0.007 P^4 < 0.0001
Doxorubicin	4 (4%)	31 (14%)	5 (5%)	26 (21%)	P^1 = 0.007 P^2 = 0.0008 P^3 = 0.75 P^4 = 0.0003
Gemcitabine	8 (8%)	35 (16%)	12 (12.5%)	23 (18%)	P = 0.08

Characteristic	Group 1 Chemo cycles in the consistent group n = 99	Chemo cycles in the non-consistent group n = 222			*P* values
		Group 2 Entire cycles n = 222	Group 2.1 Cycles with IO n = 96	Group 2.2 Cycles with no IO n = 126	
Adriamycin	8 (8%)	10 (4.5%)	3 (3%)	7 (6%)	P = 0.32
Topotecan	2 (2%)	26 (12%)	13 (13.5%)	13 (10%)	P^1 = 0.004 P^2 = 0.53 P^3 = 0.003 P^4 = 0.015
Others	4 (4%)	6 (3%)	3 (3%)	3 (2%)	P = 0.77
Consistency of integrative care¥: high	54 (54.5%)		37 (38.5%)		P = 0.031
RDI was calculated in Cycle1-Day1	68 (69%)	186 (84%)	62 (65%)	124 (98%)	P^1 = 0.03 P^2 < 0.0001 P^3 = 0.54 P^4 < 0.0001
Time interval between Cycle1-Day1 and the calculated RDI cycle* Median[25–75%]	48 [24–70]	31 [21–60]	31 [21-62.3]	34.5 [21-34.5]	P = 0.32
Cycle number between Cycle1 and the calculated RDI cycle* Median[25–75%]	3.97 ± 2.7	3.88 ± 3.26	3.97 ± 3.35	2.50 ± 0.71	P = 0.79

Characteristic	Group 1 Chemo cycles in the consistent group n = 99	Chemo cycles in the non-consistent group n = 222			*P* values
		Group 2 Entire cycles n = 222	Group 2.1 Cycles with IO n = 96	Group 2.2 Cycles with no IO n = 126	
Reasons for decreased RDI:	13 (13%)	28 (13%)	10 (10%)	18 (14%)	P = 0.69
Fatigue	6 (6%)	24 (11%)	8 (8%)	16 (13%)	P = 0.22
GI	8 (8%)	18 (8%)	11 (11.5%)	7 (6%)	P = 0.28
Pain/neuropathy	20 (20%)	54 (24%)	27 (28%)	27 (21%)	P = 0.36
Hematological	5 (5%)	18 (8%)	7 (7%)	11 (8%)	P = 0.57
Infection/fever	1 (1%)	10 (4.5%)	4 (4%)	6 (5%)	P = 0.28
Disease progression	2 (2%)	13 (6%)	8 (8%)	5 (4%)	P = 0.10
Other cause					
Total RDI Mean ± SD	0.93 ± 0.11	0.88 ± 0.16	0.89 ± 0.14	0.88 ± 0.16	P^1 = 0.005 P^2 = 1.00 P^3 = 0.098 P^4 = 0.019
% decrement in RDI in cycles with RDI < 0.97	0.14 [0.07–0.27]	0.21 [0.14–0.33]	0.21 [0.14–0.32]	0.23 [0.13–0.33]	P^1 = 0.008 P^2 = 0.644 P^3 = 0.039 P^4 = 0.009

Characteristic	Group 1 Chemo cycles in the consistent group n = 99	Chemo cycles in the non-consistent group n = 222			*P* values
		Group 2 Entire cycles n = 222	Group 2.1 Cycles with IO n = 96	Group 2.2 Cycles with no IO n = 126	
% cycles with RDI ≥ 0.97	63 (64%)	117 (53%)	50 (52%)	67 (53%)	P^1 = 0.088 P^2 = 0.89 P^3 = 0.11 P^4 = 0.13
RDI Taxanes	0.93 ± 0.10	0.87 ± 0.17	0.86 ± 0.15	0.87 ± 0.19	P^1 = 0.012 P^2 = 0.82 P^3 = 0.022 P^4 = 0.05
RDI Platins	0.93 ± 0.11	0.91 ± 0.14	0.91 ± 0.13	0.92 ± 0.14	P^1 = 0.17 P^2 = 0.67 P^3 = 0.16 P^4 = 0.38

 Group 2 subgroups relate to cycles with concomitant IO (Group 2.1) or cycles with no IO treatments (Group 2.2)

¥Continuity of integrative oncology care is considered high if ≥ 5 IO treatments within the 6 weeks succeeding the IP consultation

* In cases where cycle 1 was not selected for RDI analysis (mainly in chemotherapy cycles with concomitant integrative treatments)

AIC, Adherence to Integrative Care; RDI, Relative dose intensity

Characteristic	Group 1 Chemo cycles in the consistent group n = 99	Chemo cycles in the non-consistent group n = 222			*P* values
		Group 2 Entire cycles n = 222	Group 2.1 Cycles with IO n = 96	Group 2.2 Cycles with no IO n = 126	
P^1 = Group 1 vs. Group 2(2.1 + 2.2) P^2 = Group 2.1 vs. Group 2.2					
P^3 = Group 1 vs. Group 2.1 P^4 = Group 1 vs. Group 2.2					

Table 2 compares the chemotherapy cycles provided to Group 1 with those of group 2, as well as subgroups 2.1 and 2.2. Chemotherapy cycles and protocols (e.g., carboplation and paclitaxel) were similar in all groups with respect to the mean age of patients at the time of treatment, though patients in Group 1 were more likely to be treated with taxanes and platinum-based agents. Highly consistent IO treatment sessions was significantly more frequent in Group 1 when compared with Group 2.1 (p = 0.031).

Most of the chemotherapy cycles analyzed in subgroup 2.2 (with no IO treatments provided) included, for the most part, Cycle 1-Day 1 treatments. However, in cases where Cycle-1 was not selected for RDI analysis (mainly in chemotherapy cycles with concomitant IO treatments), the time interval between Cycle1-Day1 and the calculated RDI cycle was similar in all groups (p = 0.32). This was also evident when comparing the groups for the number of cycles between Cycle-1 and the evaluated RDI cycle (p = 0.79). Factors identified as leading to a decrease in RDI were similar in all groups, and were for the most part related to hematological toxicities (i.e., severe anemia, neutropenia and thrombocytopenia) or QOL-related concerns (severe fatigue, pain/neuropathy and gastrointestinal-related) (Table 2).

The total RDI calculated in all chemotherapy regimens analyzed was significantly higher in Group 1 when compared to Group 2 (p = 0.005), and to group 2.2 (no IO treatments) (p = 0.019). RDI was maintained more frequently in those cycles for which RDI was reduced (% decrement in RDI in cycles, with RDI < 0.97), far less in cycles where RDI was preserved (i.e., RDI > 0.97). In addition, RDI was better preserved in chemotherapy cycles with concomitant IO treatments, though this was observed with only taxane-based regimens (RDI Taxanes) in Group 1 patients when compared to Group 2 (P = 0.012), and with subgroup 2.1 (P = 0.022) and subgroup 2.2 (P = 0.05). No such advantage was observed with platinum-based regimens.

A univariate analysis using a linear regression model found greater preservation of RDI among patients who did not report pain and/or symptoms of chemotherapy-induced neuropathy (B = 0.096, 95% C.I.

0.035–0.157, p = 0.002), or among those who were consistent in their attendance of the IO treatments (B=-0.037, 95% C.I. -0.074–0.001, p = 0.047). The following formula was used for this calculation: Total RDI = 0.8**27** + 0.09**6** (if no pain-neuropathy reported) − 0.037 (if not consistent in attendance of integrative care sessions)

4. Discussion

The present study examined primarily the impact of a patient-tailored IO program on adherence to palliative chemotherapy by patients with advanced gynecological cancer, as measured by RDI. It was shown that patients who were consistent in their attendance of the IO treatments were more likely to adhere (as reflected by an RDI of > 0.97) to the planned chemotherapy regimen than those who were non-consistent in IO care. However, this finding was specific for taxane and not for platinum-based regimens. The findings of the present study also suggest that in those cycles for which RDI was reduced (RDI < 0.97), adherence was better preserved with a percent decrease of 0.14 in group 1, compared to 0.23 in group 2.2 cycles.

The relationship between IO treatments and adherence to chemotherapy regimens may reflect the ability of the IO modalities to address QOL-related concerns, such as the reduction of taxane-induced peripheral neuropathy with acupuncture. The explanation for this relationship could be that by reducing adverse effects IO treatments would thereby increase the ability of patients to tolerate the agents being administered at the planned dose. Thus, these treatments would have less of an impact on RDI when the toxicity of the agent being administered is less QOL-related, as is the case for platinum-based regimens. The hypothesis that the impact of IO treatments on RDI is a direct result of their effectiveness in reducing symptoms and improving QOL, needs to be verified in future research of this setting.

The findings presented are similar to those of a previous study which also found a correlation between IO treatments and preserved RDI among patients with mixed breast and gynecological cancers undergoing adjuvant, neo-adjuvant, and palliative chemotherapy[7]. In contrast, the present study specifically examined only patients with advanced gynecological cancers undergoing palliative chemotherapy, and analyzed both 6-week chemotherapy cycles with or without concomitant IO treatments.

There are a number of limitations to the present study which need to be addressed before any conclusions can be reached from the findings. These include the pragmatic and non-randomized methodology, which in contrast to explanatory randomized controlled trials employed a preference-controlled design in which patients were able to choose whether or not they were to receive IO treatments during all of the chemotherapy cycles (i.e., Group 1); in some of these cycles (Group 2.1); or with no concomitant IO treatment in other cycles (Group 2.2). The study groups had different baseline oncology parameters, such as higher prevalence of ovarian cancer (vs. endometrial cancer) and metastatic disease in the non-consistent IO group. And while a preference bias may have been present, the data presented in Table 1 suggest that both study groups had, for the most part, similar baseline demographic and QOL-related parameter, as well as patient attitudes toward the role of complementary medicine.

Another significant study limitation is that the consistent IO group (group 1 in Table 2) may have had a less severe degree of disease, compared to the non-consistent group (group 2, Table 2). This was suggested by the higher rates of ovarian cancer in the latter group, though metastatic endometrial carcinoma has been shown to have lower 5-year survival rates than ovarian cancer (18% vs. 30%)[7]. While the number of excluded patients due to disease progression/death was higher in the non-consistent group, as were the number of chemotherapy cycles analyzed, Table 1 shows that both groups shared similar QoL-related outcomes on EORTC and ESAS scales, as well as similar factors resulting in decreased RDI (Table 2).

It is possible, even likely, that the more severe degree of disease found in the non-consistent group may have negatively impacted the ability of patients to maintain total RDI, especially in Group 2.1 patients. Moreover, RDI within the two Group 2 subgroups (cycles with IO vs. cycles with no IO) was similar, requiring clarification through further research as to whether the IO-RDI association is specific to patients with highly advanced gynecological (i.e., stage IV ovarian) cancer. In addition, the present study did not assess QOL-related outcomes at the 6-week follow-up. Finally, the palliative care setting of the study is different from that of the neo-adjuvant/adjuvant chemotherapy setting. Here the patient's adherence to the planned chemotherapy protocol is most often determined by the disease progression and the use of additional oncology modalities (e.g., biological/immunological agents), together with or in lieu of chemotherapy drugs. In light of these limitations, the findings of the present study should be interpreted cautiously. Larger studies taking place in other oncology centers are needed to explore the generalizability and clinical significance of the present study's findings, this in real-world practice.

In conclusion, the present study suggests that a patient-tailored IO program for patients with advanced gynecological cancer may lead to a more preserved RDI effect at 6 weeks, specifically with taxane-based regimens. In contrast with the majority of IO-related research, which typically focuses on QoL-related outcomes, the present study suggests, despite its methodological limitations, that IO may also impact oncological parameters such as patients' adherence to the planned chemotherapy protocol. Additional studies are needed to explore whether the association between adherence to IO and the oncology protocol is chemotherapy-specific, particularly in patients with advanced ovarian carcinoma. Further research should not only include randomized controlled trials but also qualitative research to explore patients' and oncologists' perspectives regarding the role of IO in increasing adherence to oncology treatment protocols.

Declarations

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Conflict of Interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that they have received no support from

any organization for the submitted work, have no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years, and no other relationships or activities that could appear to have influenced the submitted work.

Availability of data and material: Data transparency is available pending to request from the submitting author

Code availability: N/A

Authors' Contributions:

EBA, NN, OG, and OL organized the trial and collected the data analyzed in this study. EBA, NN, OG, and OL planned the study. EBA, NN, OG and NS carried out the analysis and wrote a draft manuscript. All authors participated in the revision of the manuscript.

Ethics approval: The protocol of the study was approved by the Ethics Review Board (Helsinki Committee) of the Carmel Medical Center in Haifa, Israel, and was registered at ClinicalTrials.gov (NCT01860365).

Consent to participate: Participation in this study was voluntary and verified by participants' consent.

Consent for publication: All authors consented for publication of the present manuscript.

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Figures

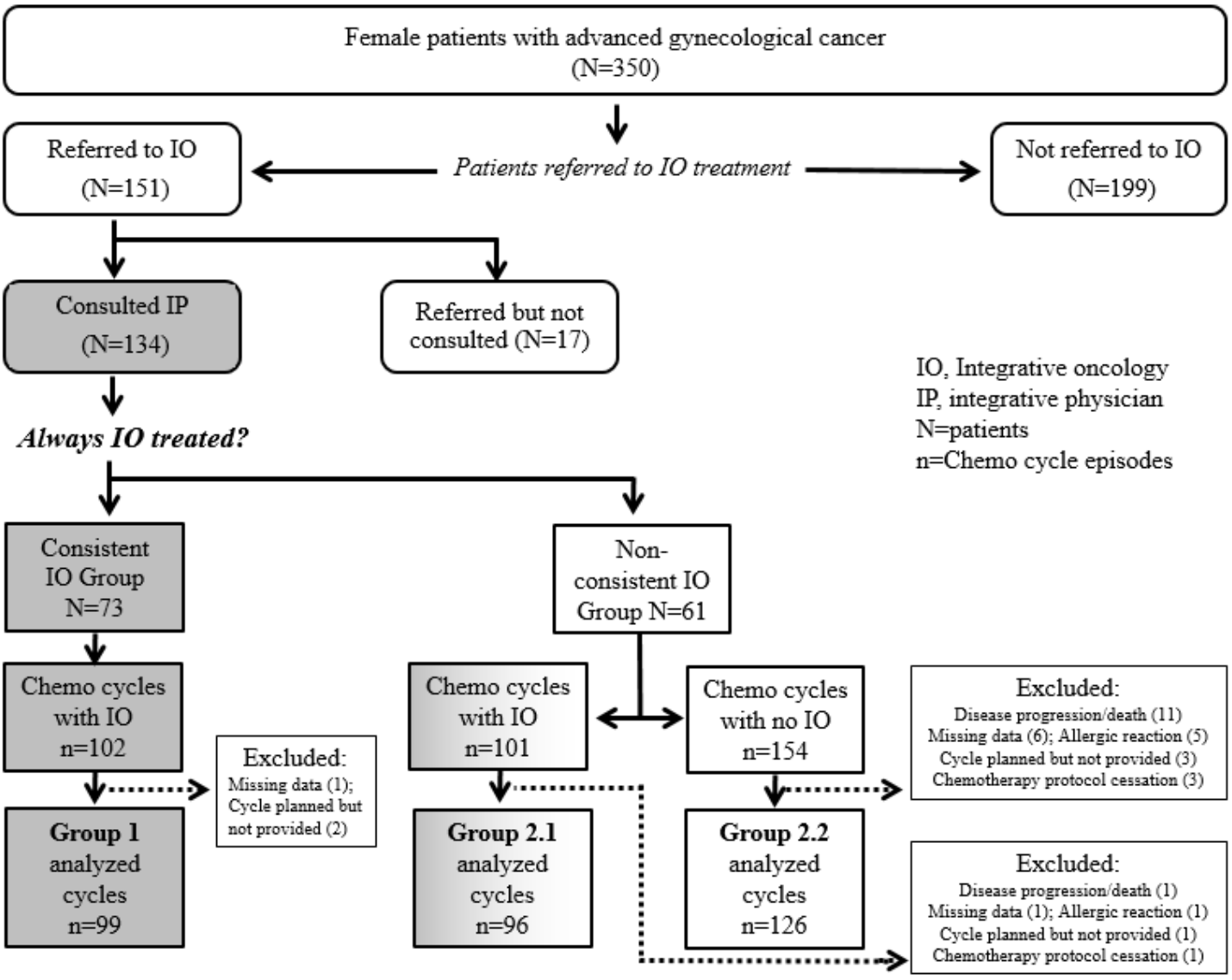
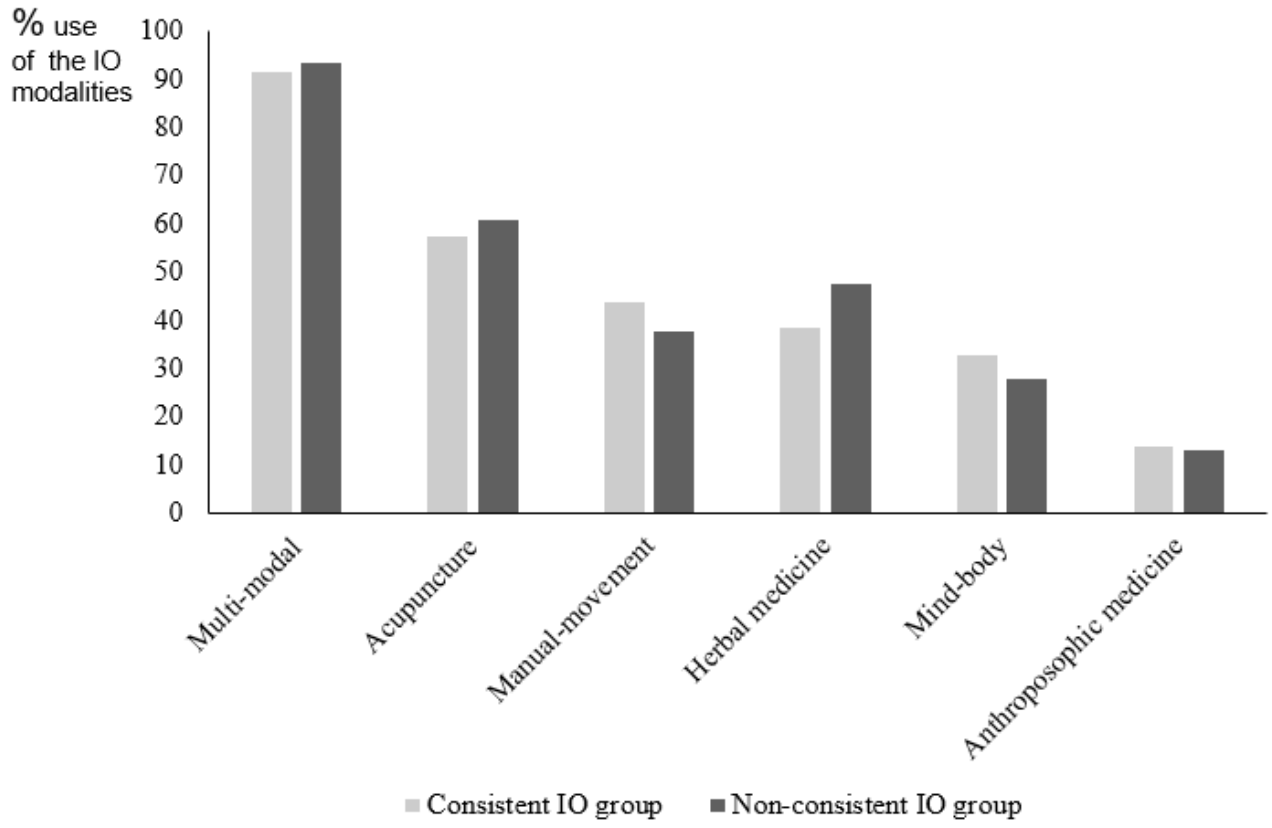


Figure 1

Patients were allocated to one of two study groups, based on their attendance at the IO treatment sessions during the 6-week study period



IO, Integrative oncology
Multi-modal > 2 IO modalities practiced simultaneously

Figure 2

Integrative medicine modalities used in the consistent and inconsistent integrative oncology groups