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Survival of patients with advanced and recurrent ovarian cancer treated using integrative medicine in Malaysia: A case series

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ABSTRACT

Background: This case series describes the survival outcomes of patients who underwent integrative medicine (IM) protocol for ovarian cancer, a treatment protocol, that integrated a carefully selected set of complementary and alternative medicine (CAM) into the conventional treatment for ovarian cancers.

Materials and methods: Retrospective review of patients' medical records was conducted at a private medical centre that delivered the IM protocol for patients with advanced and recurrent ovarian cancers. We explored and analysed the overall survival and disease progressions of those who received the IM treatment for at least 2 months.

Results: Forty patients with advanced ovarian cancers fulfilled the inclusion criteria for this case series. An overall of 75% of the cases achieved remission with initial IM treatment, 17.5% had a partial response and 7.5% showed progressive disease. The overall 5-year survival for all 40 cases is 53.1%. When explored further, the 5-year survival for cases who received CAM only is 75%, and cases who received combined limited chemotherapy with CAM had a 5-year survival of 55%. At study endpoint, 11 cases died due to ovarian cancer.

Conclusion: These findings suggest that CAM may be a valuable addition to conventional therapy to treat and improve the survival of patients with ovarian cancers. A formal randomized control trial is required to evaluate the efficacy and long-term outcomes of using IM to treat advanced and recurrent ovarian cancers.

1. Background

The long-term survival prospect for most women with advanced ovarian cancer is usually poor, despite the introduction of advanced treatment strategies and new chemotherapy regimens [1]. This is especially true for those who present at an advanced stage of cancer or present with a recurrence. Patients with advanced ovarian cancers also commonly undergo prolonged and repeated exposures to conventional chemotherapy, radiotherapy, and further surgeries following diagnosis [2].

Increasingly, complementary and alternative medicines (CAM) are being used in the treatment of this cancer [3,4]. This is done in an attempt to enhance the healing process, thus improve survival and quality of life [4,5]. Unfortunately, it is often performed without guidance from qualified experts who understand the pathophysiology of cancers and the full spectrum of cancer treatment. Nevertheless, there are some concerned practitioners who use CAM on cancer patients given the benefits that can be gained from its use. Some are used in an integrative fashion where CAM and conventional treatment are combined in the treatment strategy [6]. Combination of the two is a concept that is also known as integrative medicine (IM) [7].

An integrative medicine protocol for advanced and recurrent ovarian cancers was developed and used by a certified gynae-oncologist with 32 years' clinical experience, in a private medical centre in Malaysia. Delivery of the integrative medicine for ovarian cancer is supported by other certified health professionals such as a medical oncologist, trained nursing personnel, a nutritionist, and a chef. The medical centre is also equipped with modern technologies for the diagnosis and treatment of various cancers, and monitoring facilities which include radiotherapy, chemotherapy, positron emission tomography-computed tomography (PET-CT), operating theatre, laboratory, radiology, chemotherapy drug reconstitution unit, and rehabilitation centre.

This case series aims to report the outcomes of women with

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advanced and recurrent ovarian cancers, who opted for integrative medicine in the private medical centre as their primary treatment modality. Their survival, recurrence and remission rates, and the extent of chemotherapy usage following integrative medicine initiation were explored and described in this case series. The treatment plan for advanced and recurrent ovarian cancers in the integrative medicine protocol was also reviewed and reported. This case series will be an essential early step in evaluating whether CAM use with conventional therapy, is beneficial in improving the survival for women with advanced and recurrent ovarian cancers.

2. Materials and methods

We conducted a retrospective review of medical records for all cases that fulfilled the inclusion criteria for this case series. The medical history, treatment history, disease progressions and outcomes on the 31st January 2018 (study endpoint) of all eligible cases, were confirmed through reviews of medical records and available clinic appointment records.

2.1. Eligibility criteria of cases

Women of any age, who presented to the private medical centre between 1st January 2012 and 31st December 2017, with a diagnosis of advanced or recurrent ovarian cancer, and had received CAM from the integrative medicine protocol for at least two months, were included as cases in this case series. Cases that did not fulfil these inclusion criteria were excluded.

2.2. Description of patients who underwent the integrative medicine protocol

All the patients who underwent integrative medicine protocol in the medical centre opted for integrative medicine as their primary treatment strategy. They were of any age, diagnosed with advanced or recurrent ovarian cancer and either self-referred to the centre, or were referred by other doctors from other hospitals to receive the treatment. The patients self-funded the integrative medicine expenses as their insurance policies did not cover the CAM costs.

2.3. Description of disease progression monitoring in the integrative medicine protocol

Laboratory and imaging assessments were used to monitor patients' clinical responses in this integrative medicine protocol as practised in the conventional manner [8]. A complete response (CR) or remission was defined as the disappearance of all evidence of a tumour, including the normalisation of cancer antigen 125 (CA125) level, determined by two observations 2–4 weeks apart. Additionally, where appropriate and required, radiological evaluation such as PET-CT, magnetic resonance imaging (MRI), and ultrasonography were employed by the primary treating gynae-oncologist to establish the disappearance of the tumour. Secondary blood markers such as erythrocyte sedimentation rate (ESR), high-sensitivity C-reactive protein (hsCRP), ferritin, lactate dehydrogenase (LDH), haemoglobin A1c (HbA1c), carcinoembryonic antigen (CEA), cancer antigen 19–9 (CA19-9), and cancer antigen 15–3 (CA15-3) were used for assessment to ascertain complete response as appropriate.

When a 50% or greater decrease in the sum of the products of the perpendicular diameters of the measured lesions was observed following initiation of the integrative medicine protocol, determined by two observations not less than four weeks apart, a partial response (PR) was declared for the patient. No simultaneous increase in the size of any lesion or the appearance of new lesions was permitted, and non-measurable lesions must remain stable or regress for inclusion in this category. A patient was considered to have a stable disease when a steady state response of less than a PR or progression less than 25% lasting at least four weeks. No new lesions were to appear for inclusion in this category.

Progressive disease (PD) was defined as the unequivocal increase of at least 25% in the sum of the products of the perpendicular diameters of the measured lesions. The appearance of new lesions also constituted PD. Of note, a rise in CA125 alone was not considered to be PD unless there were other accompanying changes seen in PET-CT, MRI, ultrasonography, and other secondary markers such as ESR, hsCRP, ferritin, LDH, HbA1c, CEA, CA19-9, and CA15-3.

2.4. Description of the CAM components in the integrative medicine protocol

Six types of CAM modules were integrated into the conventional treatment for ovarian cancers. The six CAM modules are:

a) CAM module 1: Specific anti-cancer treatment
b) CAM module 2: Modulation of the immune system therapy
c) CAM module 3: Detoxification and optimisation of metabolic function
d) CAM module 4: Nutritional therapy
e) CAM module 5: Lifestyle modification
f) CAM module 6: Psycho-neuroendocrine immunology

Please refer to Appendix 1: CAM modalities and list of therapies.

The first three modules included prescription and administration of substances that are formally and informally labelled as nutritional supplements or herbal products, aiming at the specific intended effect as the module titles suggest. The gynae-oncologist made the prescriptions for CAM treatment from these modules and administered the CAM in the treatment facility.

The other three CAM modules required counselling sessions which were delivered by a nutrition specialist, a chef, and the gynae-oncologist. The integrative medicine protocol for ovarian cancer was managed by the primary treating gynae-oncologist, and jointly delivered by other health care professionals in the centre for all the patients.

2.5. Description of delivery and approach of the integrative medicine protocol

Before undergoing the treatment, each patient had her disease condition thoroughly investigated and explained by the gynae-oncologist and medical oncologist. All treatment options for both the conventional and integrative medicine protocols were also explained in detail. The treatment process began only after the patients consented to undergo the integrative medicine protocol.

The protocol began with the induction of CAM, where each CAM module was introduced and administered to the patients sequentially. Where indicated, tumour debulking and removal or excision surgeries were performed first. The same gynae-oncologist performed all surgeries for patients who required surgeries. Alkaline peritoneal lavage was an additional procedure performed intraoperatively by the gynae-oncologist during the surgeries. The induction of CAM was done early in the treatment and continued postoperatively.

Following induction of CAM (post CAM induction), patients' clinical responses were monitored and evaluated by the gynae-oncologist using the monitoring process as described in section 2.3 "Description of disease progression monitoring in integrative medicine". Based on the clinical responses post CAM induction, the gynae-oncologist determined whether the patients needed chemotherapy, radiotherapy, or further surgery.

Patients who showed favourable clinical responses post CAM induction were not indicated for chemotherapy, and therefore continued the treatment with CAM only. While receiving CAM, the patients continued to be monitored closely. Their treatment approach only changed if the disease progressed.

Patients with less favourable clinical responses post CAM induction,

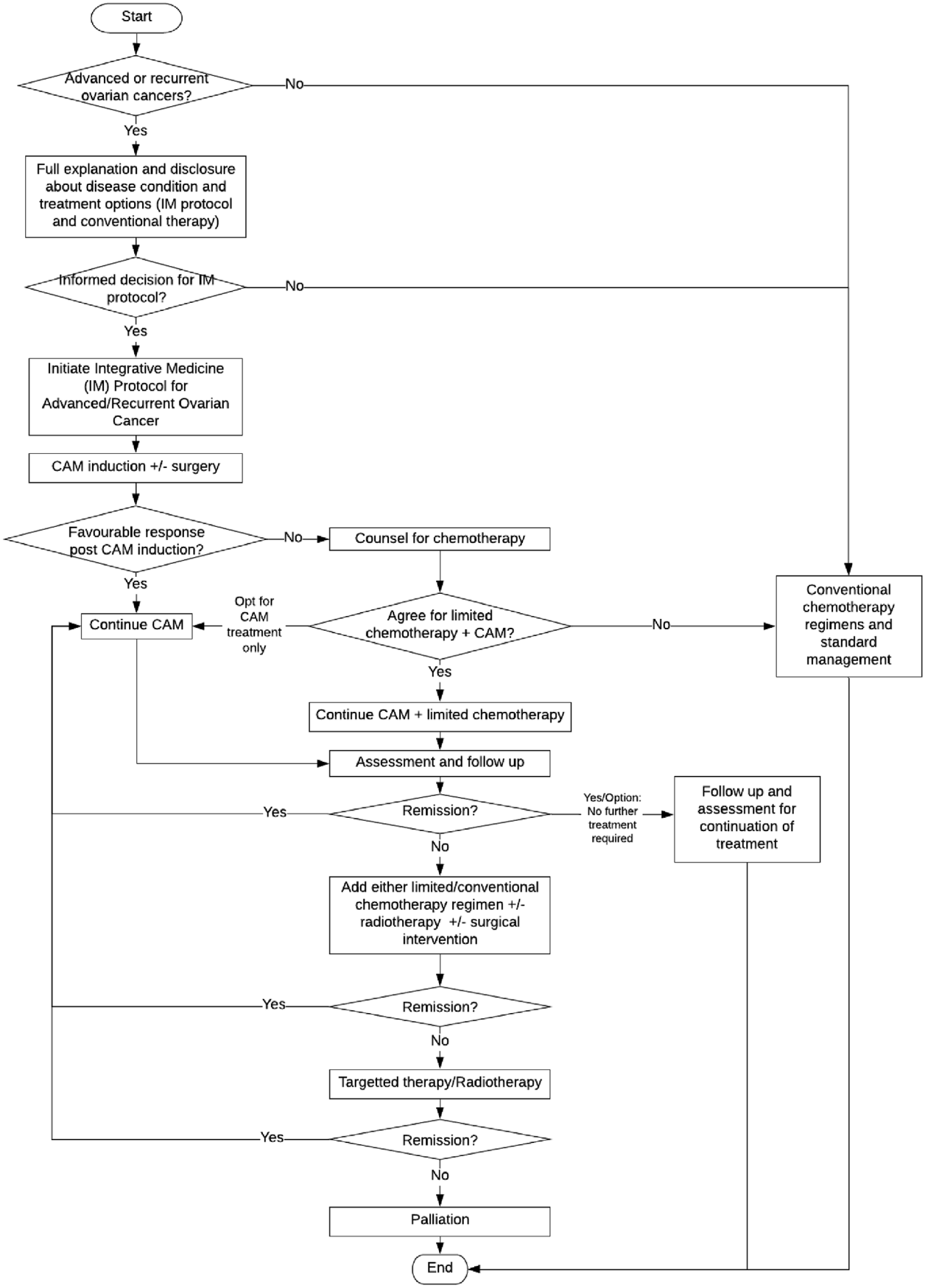

Fig. 1. Flow diagram of the integrative medicine treatment plan for ovarian cancer.
Abbreviations: CAM, Complementary and alternative medicine.

on the other hand, were offered either full dose chemotherapy as per standard ovarian cancer regimen, or limited single-agent chemotherapy with CAM. These patients received continuous monitoring during the chemotherapy administration, and the chemotherapy treatment was either escalated, de-escalated, or stopped based on their clinical responses. Further interventions such as radiotherapy or surgical interventions were instituted depending on the progression of the disease.

Overall, the treatment approach used in the integrative medicine protocol for ovarian cancer generally follows the conventional treatment approach for any cancer treatment. Surgery, chemotherapy, and radiotherapy, which are the standard strategies used to destroy and eliminate cancer cells, were not omitted from the treatment plan. The flow diagram of the integrative medicine treatment plan for ovarian cancer is illustrated in Fig. 1.

2.6. Statistical analysis in this case series

Some of the outcomes in this case series were described through statistical analysis. Proportion and central tendencies were analysed using descriptive statistical analysis. Kaplan-Meier estimate was used to describe the overall survival of the patients, and survival outcomes by treatment types and cancer stage. Overall survival is defined as the time from the initiation of integrative medicine to the time of death due to ovarian cancer. The event of interest in the survival analysis is death due to ovarian cancers. Cases who remained alive, lost to follow-up or experienced death due to other causes by 31st January 2018 were censored.

3. Results

3.1. Overall demography and disease background

A total of 76 patients were identified to receive integrative medicine in the medical centre for the treatment of ovarian cancer. Forty patients fulfilled the eligibility criteria of cases and hence were included in this case series. Thirty-six other patients were excluded from the analysis as the duration of integrative medicine treatment received by these patients was less than two months, or they had cancers at earlier stages (stage 1 or stage 2). There was no loss to follow-up in the 40 included cases.

Most of the cases were Malaysian citizens (60%), followed by Indonesian (37.5%) and China Chinese (2.5%). Majority presented to the centre with primary ovarian cancer stage 4 (35%), followed by stage 3 (32.5%). The remaining 32.5% presented with recurrent ovarian cancer and had received prior treatment in the past. Their overall mean age was 45.7 years (standard deviation, SD 13.1), and most belonged to the 50–59 years age group (42.5%).

Serous carcinoma (40%), endometrioid carcinoma (22.5%) and clear cell carcinoma (17.5%) were the most prevalent types of ovarian cancers seen among these cases. This was followed by mucinous cystadenocarcinoma (5%), carcinosarcoma (2.5%), granulosa cell tumour (2.5%), sarcoma (2.5%), transitional cell carcinoma (2.5%), and urothelial neoplasm (2.5%).

Fifty per cent of all the cases had a poorly differentiated cancer, 45% had moderately differentiated cancer, 2.5% had well-differentiated carcinoma, and 2.5% unspecified histological grade. The cases demographics, types of ovarian cancers, and disease staging distributions are shown in Table 1. All of the 40 cases were treated, followed up, and observed for disease progression by the same gynae-oncologist.

3.2. Compliance to the integrative medicine protocol

Of the 40 cases, 35 were compliant to the protocol. The remaining 5 decided to discontinue the protocol after receiving CAM induction for two months and subsequently underwent a conventional chemotherapy regimen. These 5 cases continued their treatment under the care and followed up by the medical oncologist in the centre. The reason for opting out of the integrative medicine was generally due to financial constraints as the CAM treatments were not covered in their insurance policies.

Table 1
Demographics, types of ovarian cancers and staging at first presentation.

Cases characteristics	Mean (SD)	Frequency n (%)
Age (Completed Years)	45.7 (13.1)	
20-29		7 (17.5%)
30-39		4 (10.0%)
40-49		9 (22.5%)
50-59		17 (42.5%)
> 60		3 (7.5%)
Citizenship		
Malaysian		24 (60.0%)
Indonesian		15 (37.5%)
China		1 (2.5%)
Types of ovarian cancer		
Serous carcinoma		16 (40%)
Endometroid adenocarcinoma		10 (25%)
Clear cell carcinoma		7 (17.5%)
Mucinous cystadenocarcinoma		2 (5%)
Carcinosarcoma		1 (2.5%)
Granulosa cell tumour		1 (2.5%)
Sarcoma		1 (2.5%)
Transitional cell carcinoma		1 (2.5%)
Urothelial neoplasm		1 (2.5%)
Stage of disease upon presentation		
Stage 3		13 (32.5%)
Stage 4		14 (35.0%)
Recurrence		13 (32.5%)

Abbreviations: SD, standard deviation.

3.3. Initial clinical response post CAM induction

Following CAM induction (with or without debulking surgeries), 22 of the 40 cases showed favourable clinical responses (remission). These cases, therefore, were not planned for any chemotherapy but continued their treatment with CAM only.

The other 18 cases had unfavourable responses (partial response) following debulking surgeries and CAM induction. Of the 18, 5 cases discontinued integrative medicine and proceeded with conventional chemotherapy regimen for the treatment of their advanced and recurrent ovarian cancers. The remaining 13 cases were planned for limited chemotherapy administration, given their partial responses to CAM induction. One of the cases, however, refused to receive any chemotherapy and continued with CAM treatment alone. The other 12 cases who showed unfavourable responses post CAM induction, received combined limited chemotherapy with CAM. Fig. 2 illustrates the observed clinical responses among all the cases post CAM induction.

3.4. Observed disease progressions post CAM induction

3.4.1. Disease progression for cases who received CAM only

This group comprised of 22 cases who responded well to CAM induction, and 1 case who refused chemotherapy despite having an unfavourable response. Ten of these cases presented with cancer stage 3, while 5 presented with cancer stage 4, and the remaining 8 cases presented with recurrence. Their median age was 48 years (interquartile range, IQR 19).

The 22 cases who responded well to CAM induction at the beginning of the treatment, continued with CAM only as initially planned. With CAM treatment alone, 20 of the 22 cases, achieved complete response or remission. The remaining 2 cases did not achieve remission with CAM alone. Both had a partial response and proceeded to receive limited chemotherapy with CAM subsequently.

The one case with an unfavourable response to CAM induction, who

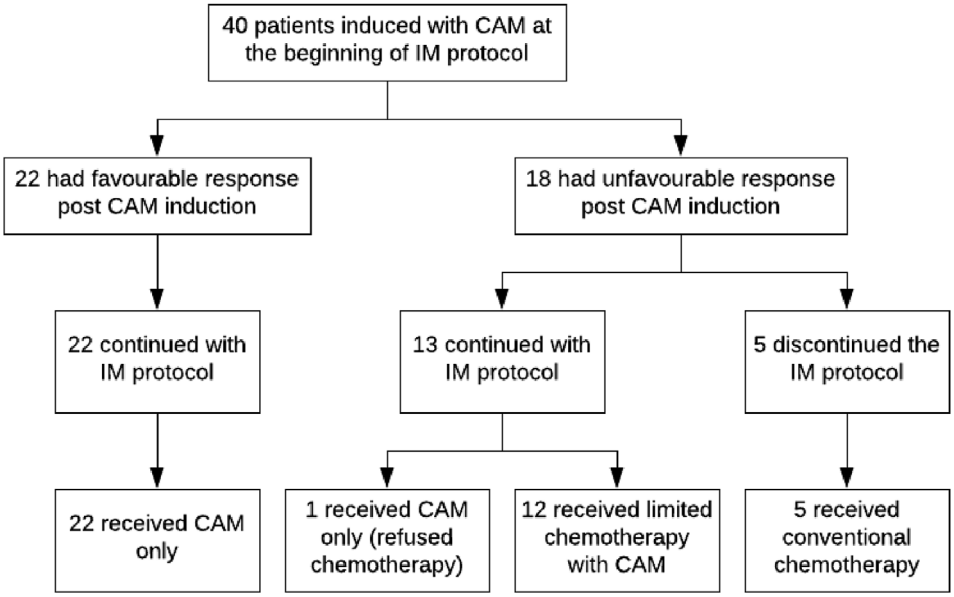

Fig. 2. Clinical responses post CAM induction.
Abbreviation: CAM, Complementary and alternative medicine; IM, Integrative medicine.

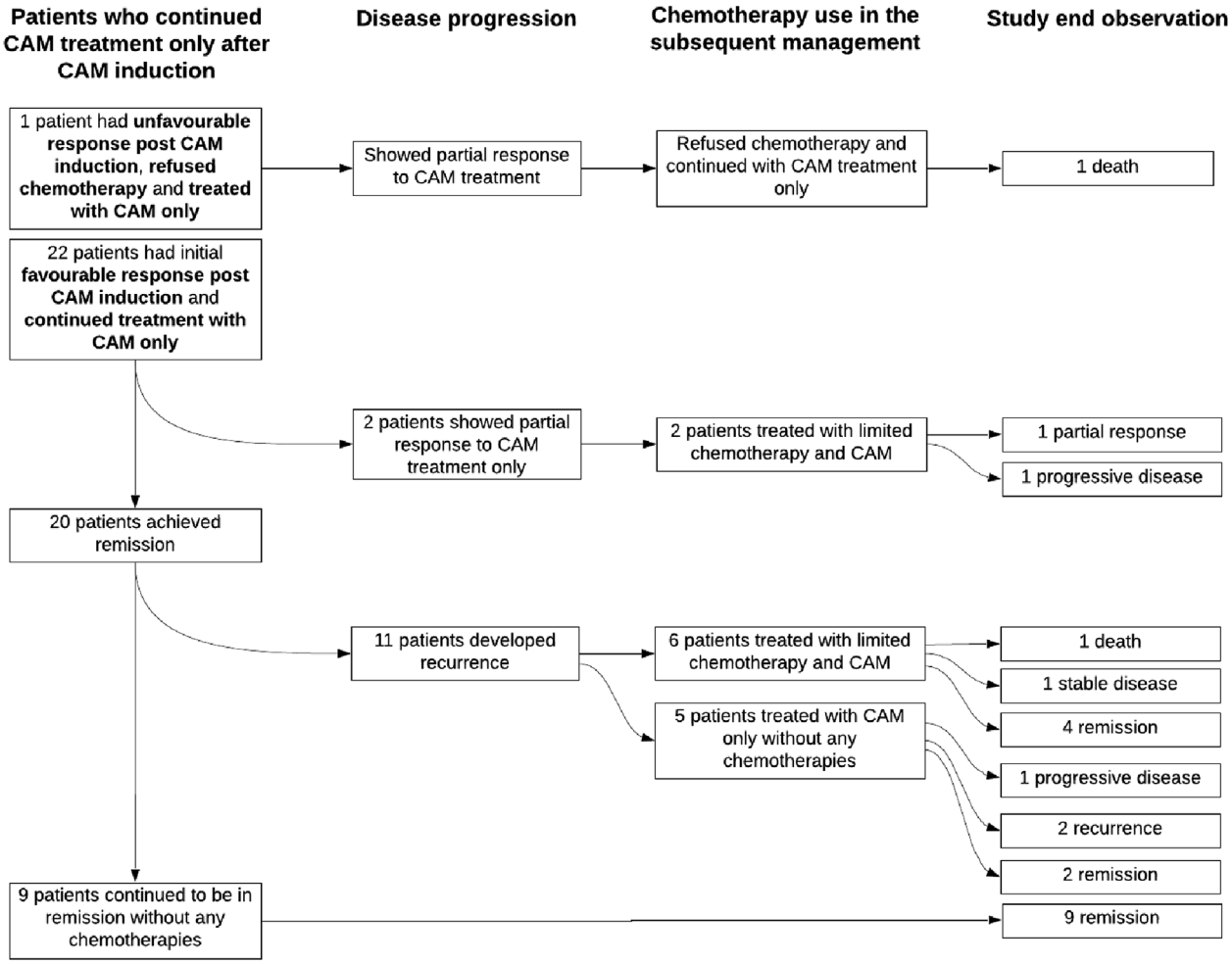

Fig. 3. Disease progressions of 23 cases who received CAM only post induction.
Abbreviation: CAM, Complementary and alternative medicine.

refused limited chemotherapy and continued with CAM treatment only, showed a persistent partial response. Please refer to Fig. 3. Disease progressions of 23 cases who received CAM alone post induction.

3.4.2. Disease progression for cases who received combined limited chemotherapy with CAM

This group comprised of 12 cases who had unfavourable clinical responses post CAM induction. Three of the cases presented with cancer stage 3, while 5 presented with cancer stage 4 and the remaining 4 cases presented with recurrence. Their median age was 54.5 years (IQR, 21). All were planned for early chemotherapy and received combined limited chemotherapy with CAM. With this treatment combination, 8 of them achieved remission, 2 persisted with partial response, and 2 had progressive disease.

3.4.3. Disease progression for patients who opted for conventional chemotherapy

This group comprised of the 5 cases who had unfavourable responses to CAM induction and discontinued integrative medicine. Four of these cases presented with cancer stage 4, and 1 presented with recurrence. Their median age was 52 years (IQR, 16.5). They received the conventional chemotherapy regimen after CAM induction. Following that, 2 of them achieved remission, 2 persisted with partial response, and 1 had progressive disease.

3.5. Overall remission, recurrence and chemotherapy usage

Overall, 30 (75%) patients who received CAM for at least two months upon initiation of treatment achieved remission, while 7 (17.5%) had a partial response, and 3 (7.5%) showed progressive disease. Table 2 shows the disease progression and recurrences among cases inducted with CAM according to subsequent treatment.

Table 2
Disease progression and recurrences among cases inducted with CAM according to treatment groups.

	Group 1 (n = 23) [n (%)]	Group 2 (n = 12) [n (%)]	Group 3^ (n = 5) [n (%)]	Overall (n = 40) [n (%)]
Disease progression+				
Remission	20 (87)	8 (66.6)	2 (40)	30 (75)
Partial response	3 (13)	2 (16.7)	2 (40)	7 (17.5)
Progressive disease	0	2 (16.7)	1 (20)	3 (7.5)
Average duration to achieve remission*+ (in months)				
Mean (SD)	3.52 (7.5)	4.33 (1.7)	4.67 (4.1)	3.7 (6.4)
Median (IQR)	2.0 (2)	4.0 (2)	4.0 (0)	4 (3)
Recurrence rate (100p-y)	27.0	29.4	42.6	29.1
Disease progression at study endpoint				
Remission	15 (65.2)	5 (41.7)	0	20 (50)
Partial response	1 (4.3)	0 (0)	0	1 (2.5)
Stable	1 (4.3)	1 (8.3)	0	2 (5)
Progressive disease	2 (8.7)	1 (8.3)	0	3 (7.5)
Recurrence	2 (8.7)	1 (8.3)	0	3 (7.5)
Death	2 (8.7)	4 (33.3)	5 (100%)	11 (27.5)

^ Discontinued the IM protocol + First observation *Among those who achieved remission.

Group 1: Cases who received CAM only. Group 2: Cases who received limited chemotherapy with CAM. Group 3: Cases who received conventional chemotherapy. The total person-years in Group 1 is 66.6 years, and recurrence frequency observed in this group is 18. The total person-years in Group 2 is 27.25 years, and recurrence frequency observed in this group is 8. The total person-years in Group 3 is 9.4 years, and recurrence frequency observed in this group is 4. Abbreviation: CAM, Complementary and alternative medicine; IM, Integrative medicine; SD, Standard deviation; Med, Median; IQR, Interquartile range.

Table 3
Types and number of chemotherapy cycles received by cases.

Types of chemotherapy	Number of chemotherapy cycles received by cases	
	Continued with integrative medicine (n = 20)	Discontinued integrative medicine (n = 5)
Single-agent		
Carboplatin	73	18
Zomikal	0	2
Navelbin	0	1
Gemcitabine	0	1
Avastin	0	7
Caelyx (Pegylated liposomal doxo)	0	1
Double agent		
Paxus/Carboplatin	0	22
Gemcitabine/Carboplatin	0	1
Paxus/Gemcitabine	0	1
Cisplatin/Etoposide	0	2
Cisplatin/Paclitaxel	0	2
Caelyx/Gemcitabine	0	1
Triple agent		
Paclitaxel/Gemcitabine/ Avastin	0	2
Paclitaxel/Carboplatin/Avastin	0	9
Carboplatin/Doxo/ Cydophosphamide	0	1

The proportion of cases that attained remission was the highest among those who continued the treatment with CAM only (87%). The median duration to achieve remission among cases treated with CAM only was 2.0 months and 4.0 months for cases treated using limited chemotherapy with CAM and conventional chemotherapy. The recurrence rate among those who continued the treatment with CAM only is 27 per 100 person-years. Cases treated using limited chemotherapy with CAM had a recurrence rate of 29.4 per 100 person-years. Those who discontinued CAM and received conventional chemotherapy had a recurrence rate of 42.6 per 100 person-years.

Overall, 20 of the 35 cases who were compliant to the integrative medicine protocol, received limited chemotherapy either due to a partial response to CAM induction, or recurrence of cancer after attaining prior remission. All of these 20 cases received only single-agent chemotherapy. The overall number of chemotherapy cycles used by these cases was lesser compared to the 5 cases who discontinued the protocol. The 5 cases received up to 3 types of chemotherapy agents. The types and number of chemotherapy cycles received by the cases are shown in Table 3.

3.6. Overall survival

The median duration of follow-up for all 40 cases was 29.5 months (IQR 28, min 2, max 71), by which point 7 of the 40 had died. The 5-year overall survival for all the cases is 53.1%. Further exploration found that the 5-year survival for the 23 cases who received CAM only post induction was 75%, while the 12 cases who received limited chemotherapy with CAM had a 5-year survival of 55%. The observed overall survival for cases who discontinued the integrative medicine protocol and received conventional chemotherapy was lower than those who continued with the protocol (median survival 27 months; 95% CI 20.6, 33.4). Please refer to Fig. 4 for the survival curves of three different groups of cases, and Table 4 the overall survival and survival rates according to groups.

Survival curves according to cancer stage were also explored. Fig. 5

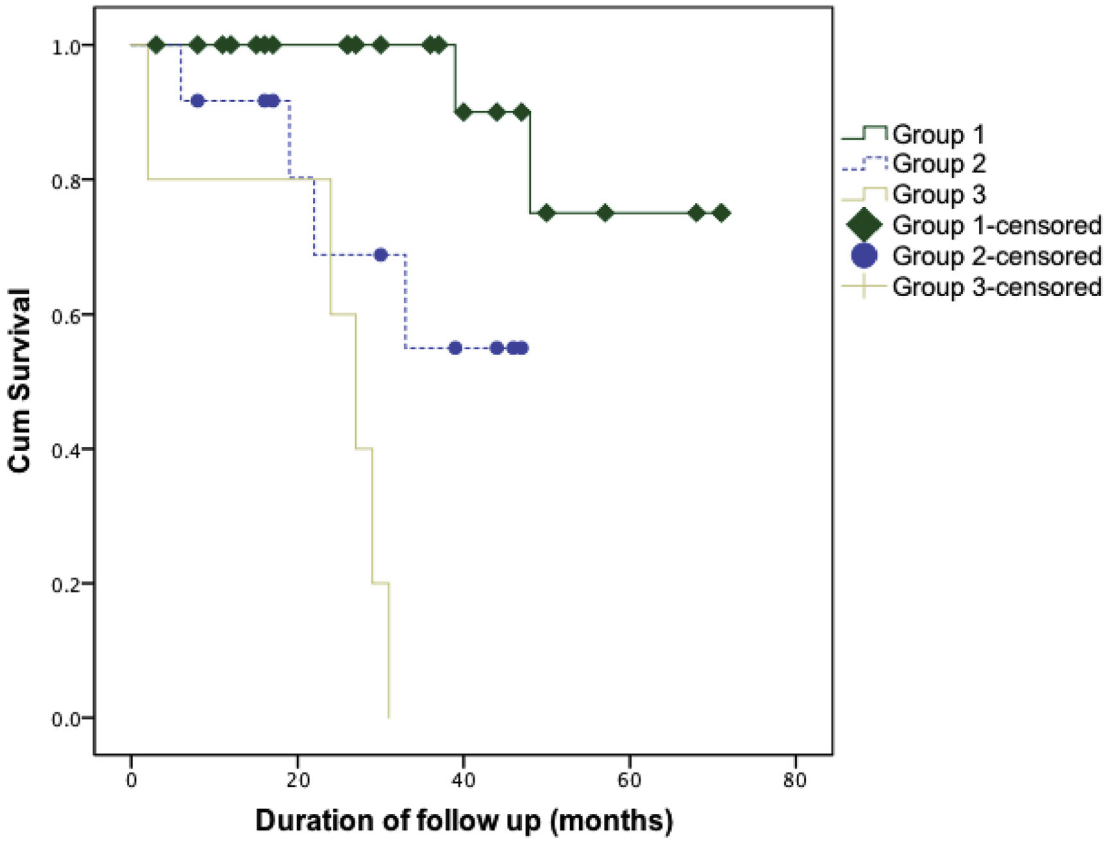

Fig. 4. Survival curves for three different groups of cases.
Group 1: Cases who received CAM only. Group 2: Cases who received limited chemotherapy with CAM. Group 3: Cases who received conventional chemotherapy.

Table 4
Overall survival and survival according to groups.

Survival variables	Overall (n = 40)	According to groups		
		Group 1 (n = 23)	Group 2 (n = 12)	Group 3 (n = 5)
Median overall survival (95% CI)	–	–	–	27 months (20.6, 33.4)
75th percentile survival (SE)	–	48 months (0.0)	22 months (3.994)	24 months (24.1)
Percentage of survival				
Survival 1 year	94.9%	100%	91.7%	80%
Survival 2 year	84.8%	100%	68.8%	60%
Survival 3 year	68.6%	100%	55%	0%
Survival 4 year	53.1%	75%	55%	0%
Survival 5 year	53.1%	75%	55%	0%

Group 1: Cases who received CAM only. Group 2: Cases who received limited chemotherapy with CAM. Group 3: Cases who received conventional chemotherapy. Abbreviation: CAM, Complementary and alternative medicine; SE, Standard error; CI, Confidence intervals.

illustrates the survival curves for all cases according to cancer stage.

3.7. Outcomes for cases with recurrent ovarian cancer

Thirteen cases with recurrent ovarian cancer received CAM for at least two months. One of them discontinued the integrative medicine protocol and received conventional chemotherapy. The remaining 12 cases continued with the integrative medicine protocol. Of the 12 cases, 8 showed favourable response post CAM induction thus continued the treatment with CAM only. The remaining 4 showed unfavourable responses, received limited chemotherapy with CAM thereafter.

Two deaths were observed among these 12 recurrent cases who continued with integrative medicine at the study endpoint. Of those who remained alive (10), 4 achieved remission with CAM treatment only and remained in remission until the study endpoint. Five others received limited chemotherapy with CAM where at the end, 1 achieved remission, 2 developed stable disease, 1 had a recurrence, and 1 had progressive disease. One case achieved remission with CAM treatment alone but developed a recurrence at the study endpoint. Please refer to Fig. 6 for illustration of disease progression among cases with recurrent ovarian cancer. The overall 5-year survival for cases with recurrent ovarian cancer who continued with integrative medicine was 74.0%.

3.8. Case studies to illustrate a variety of clinical situations

3.8.1. *Outcome for a case of reproductive age with advanced ovarian cancer (fertility preservation)*

A 20-year old Malaysian woman presented to the medical centre with stage 3 serous papillary cystadenocarcinoma in February 2012, and with a pre-operative CA125 level greater than 32,000 U/mL. She underwent the integrative medicine protocol where she received CAM induction and underwent exploratory laparotomy. Left salpingo-oophorectomy, omentectomy and para-aortic lymph nodes dissection were performed, and her reproductive organs (one of the ovaries and uterus) were preserved during the surgery. Intra-peritoneal alkalisation was performed following the exploratory laparotomy.

She showed favourable clinical response following CAM induction and surgery, hence continued with CAM treatment without any chemotherapy. Two months following the surgery, she achieved remission and her CA125 level normalised.

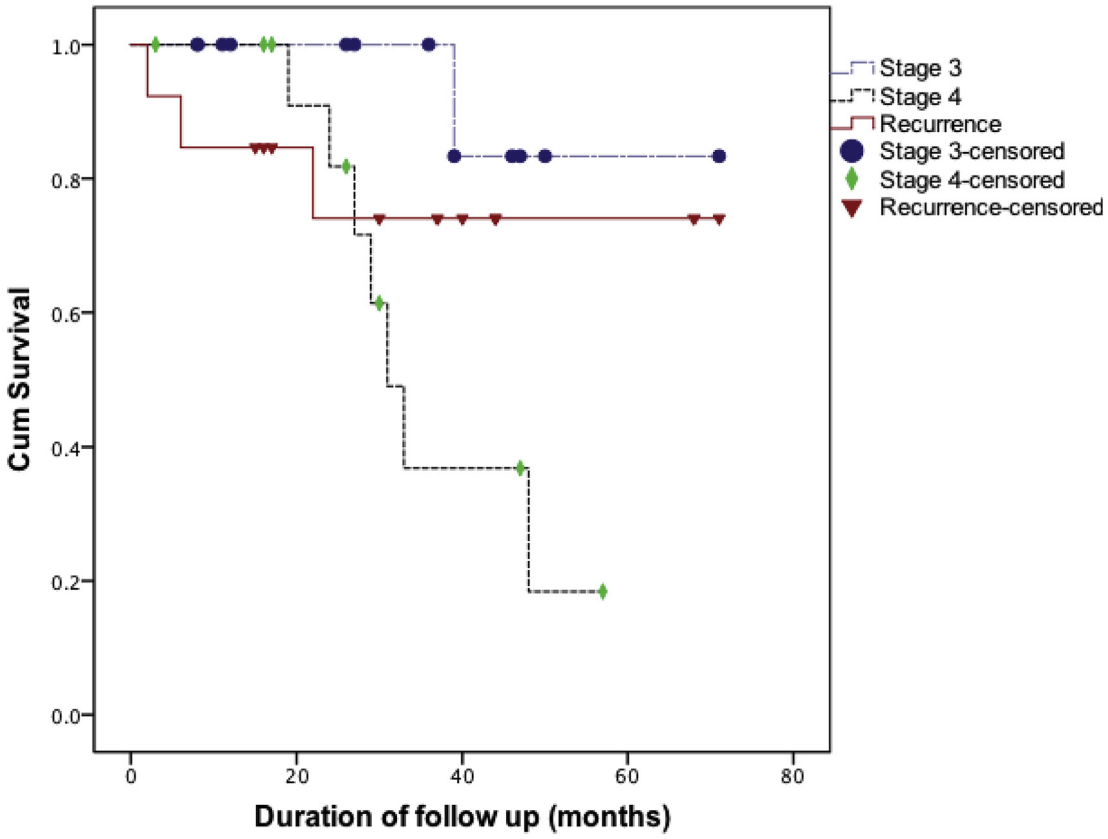

Fig. 5. Survival curves for all reviewed cases according to cancer stage.

Her first pregnancy after remission ended in a miscarriage. She had a successful second pregnancy, and her first child was born in 2014. In November 2016, she became pregnant for the third time. It was an uneventful pregnancy, and she underwent normal labour. She delivered another healthy child in September 2017. She continued receiving CAM treatment and was still in remission at the study endpoint.

3.8.2. ***Outcome of a palliative case*** *(function preservation)*

A 48-year old Indonesian woman presented to the medical centre in April 2012 with recurrent serous papillary cystadenocarcinoma. Before her presentation to the medical centre, she had undergone multiple prior surgeries and chemotherapy. Due to the recurrence and extent of the cancer, she was considered for palliation.

She sought CAM for the treatment of her cancer in the medical centre. She was induced with CAM treatment immediately at presentation and underwent debulking surgery with reconstruction of the bladder and right ureter. The surgery removed 90% of the recurrent solid tumour. Some residual tumours were left unoperated to preserve bowel function. Intra-peritoneal alkalisation was performed post-operatively.

She continued with CAM treatment post-surgery and showed a positive clinical response, therefore, did not require any chemotherapy. She achieved remission five weeks later (June 2012) and continued to be in remission for 29 months before the cancer recurred. The cancer recurred as abdominal wall solid tumour recurrence. She was treated with wide local surgical excisions and metabolic therapy. She did not receive any chemotherapy or radiotherapy throughout the treatment and follow-up. She had another localised abdominal wall recurrence in November 2017 (confirmed via PET scan) and this was excised. She continued with the CAM treatment and was in remission at the study endpoint.

3.8.3. Outcome of a case with ovarian cancer stage 4 and limited use of chemotherapy

A 42-year-old Malaysian woman was diagnosed with stage 4 ovarian cancer in February 2016. She initially sought treatment in 2 other gynae-oncological centres and was offered the choice of debulking surgery and adjuvant chemotherapy. She declined the options and sought self-therapy (alternative treatment). Initially, positive responses from the self-therapy such as resolution of ascites and decreasing tumour marker levels were observed. The tumour marker levels decreased and plateaued but did not achieve remission level. At that juncture, in September 2016, she sought integrative medicine treatment at the private medical centre.

She agreed for a debulking surgery after consulting the gynae-oncologist, and the surgery was performed in October 2019. Her serial CA125 levels did not normalise following the surgery and after receiving nutritional and metabolic therapies (CAM). She was then advised for adjuvant chemotherapy with CAM. She received single chemotherapy agent (carboplatin) with concurrent high dose parenteral sodium ascorbate (vitamin C) and anti-oxidants in December 2016. Her tumour markers normalised 4 weeks after the administration of one dose of carboplatin. The patient declined further chemotherapy following that, and carboplatin administration was stopped after the first dose was completed. She continued with the CAM treatment and remained to be in remission at the study endpoint.

4. Discussion

This case series identified several key findings pertaining to the use of CAM in ovarian cancer treatment. Integration of the selected CAM into conventional ovarian cancer therapy appeared to be beneficial in the clearance of cancer cells and patients' survival. Patients with advanced and recurrent ovarian cancers who continued to receive monitored and structured CAM treatment had a high overall 5-year survival

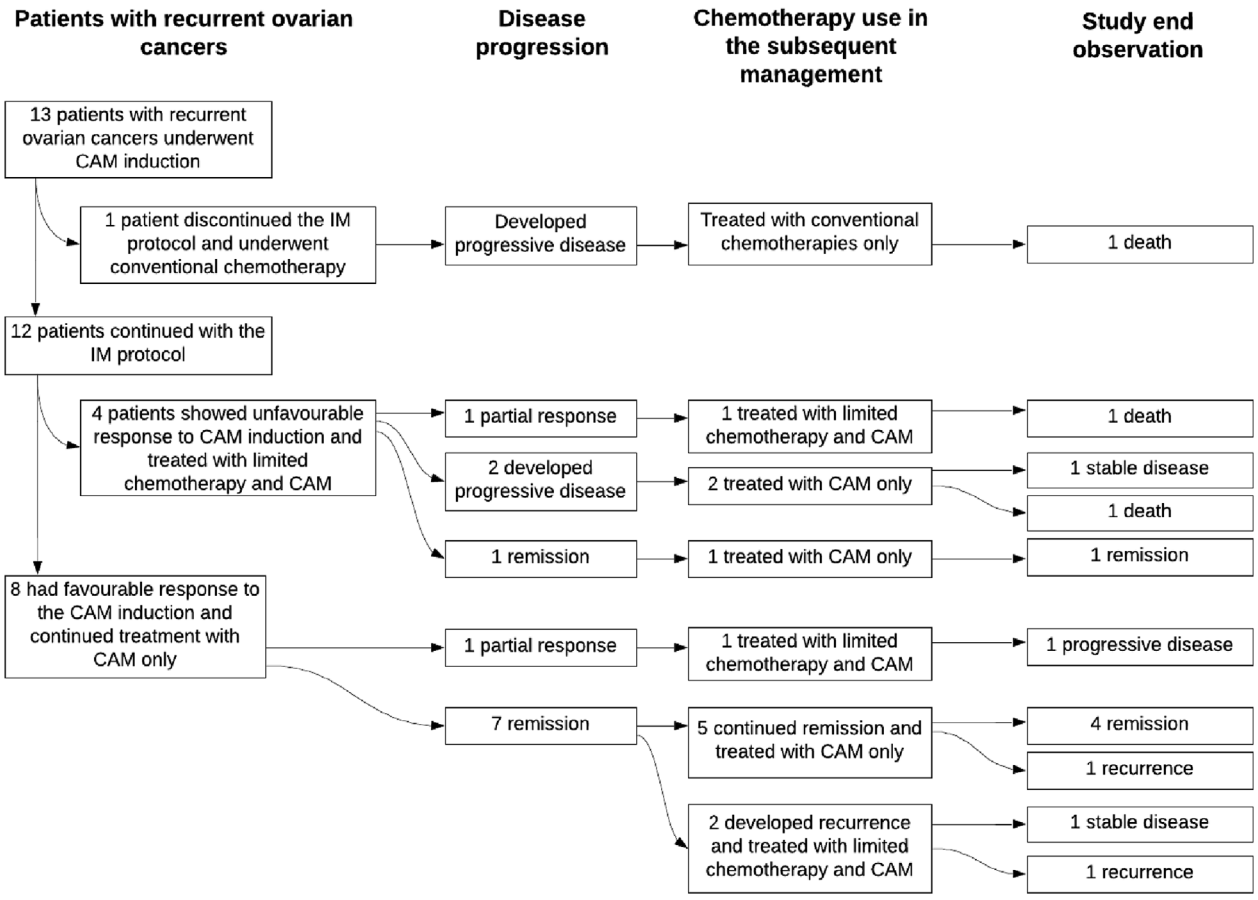

Fig. 6. Disease progression among cases with recurrent ovarian cancer.
Abbreviation: CAM, Complementary and alternative medicine; IM, Integrative medicine.

rate. Although all of those who discontinued the integrative medicine died by the third year of treatment, most of the other patients were alive at the study endpoint (82.9%).

The induction of CAM at the initial stage of treatment in the integrative medicine protocol also resulted in early remission in a substantial number of patients. Despite the advanced stage of their cancer, with continuous CAM treatment, some patients remained in remission without the need for any chemotherapy. When CAM alone was inadequate to achieve remission, its combined use with low doses of conventional chemotherapy showed positive outcomes for most of the patients. There is also a small number of patients who presented with recurrent cancer that were able to achieve remission by using CAM only.

Another important key finding in this case series is the amount of chemotherapy used in the integrative medicine protocol. The number of chemotherapy agents and cycles used were lower among patients who continued their treatment with the integrative medicine protocol. The chemotherapy used to achieve complete remission among patients who used conventional cancer therapy, is considerably greater in terms of the number of cycles used and combination of agent types.

We compared the survival data found in this case series with other published ovarian cancer survival data as a crude method to evaluate the performance of the integrative medicine protocol. The 5-year survival rate for ovarian cancers in the United Kingdom (UK) at stage 3 was 18.6% and at stage 4 was 3.5%. These rates were based on the published data from Cancer Research United Kingdom (Cancer Statistic for Ovarian Cancers) [9]. The National Cancer Institute, Surveillance, Epidemiology, and End Results United States (SEER US) on the other hand, reported and published the 5-year survival rate for cases in the US with distant ovarian cancer as 29.2% [10]. In this case series, patients with advanced ovarian cancer (stage 3 and stage 4) who underwent the integrative medicine for at least two months, had a 5-year survival rate of 53.1%. Overall, the 5-year survival rate for those who continued to receive CAM in the integrative medicine protocol, is notably higher when compared to other survival data for advanced ovarian cancers.

To explain the observations above, we explored plausible mechanisms and roles of CAM used in the integrative medicine protocol in cancer treatment. One of the CAM modules used in the protocol is multi-nutrients supplementations to the patients. The multi-nutrients supplementation possibly replenished depleted macro and micro-nutrients associated with cancer patients. This may have resulted in an improved immune system and well-being for the recipients, which augmented natural clearance of cancer cells [11].

Another plausible explanation may be elucidated through the work of a study that examined the use of high dose parenteral ascorbate in ovarian cancer [12]; one of the CAM used in the integrative medicine protocol. This study demonstrated that high-dose parenteral ascorbate reduced chemotherapy-associated toxicity in ovarian cancer patients. It also demonstrated the synergistic action of ascorbate with carboplatin and paclitaxel in preclinical ovarian cancer models, and explained the mechanism of ascorbate-induced cytotoxicity in ovarian cancer cells. Another previous study also found a similar result where anti-tumour activity was seen in ovarian cancer cells following high dose ascorbate administration [13]. High dose ascorbate used in the integrative medicine protocol may have worked synergistically with the chemotherapy used in the treatment for the patients seen in this case series.

Besides high dose parenteral ascorbate, melatonin and amygdalin were other substances used in the protocol that also have apoptosis-inducing and cytotoxic effects in cancer cells [14–19]. These studies

found that their use is associated with improved quality of life and survival rates for cancer patients as well. Patients in this case series may have benefited from the use of these CAM, possibly through a similar mechanism of action.

The integrative medicine protocol also included a module that addressed cancer as part of a metabolic disorder. The inclusion of such module is mainly due to the emerging evidence indicating that cancer is primarily a metabolic disease involving disturbances in energy production through cellular respiration and fermentation [20]. Besides, environmental factors leading to dysregulation of cellular metabolic mechanisms also have been identified to be responsible for the epigenetics in cancer development [21–23]. Therefore, CAM that produces cellular metabolic shift as another pathway for cancer treatment was included in the integrative medicine protocol [24,25].

The selected CAM that addressed cancer as a metabolic disorder possibly caused a cellular shift that balanced metabolic disequilibrium following its administration. The benefits of cellular metabolic shift, as found by several studies, may have resulted in cancer cells lysis, enhanced normalisation and metabolic efficiency of healthy cells and subsequently, improved the overall general health of the patients [20,26–28]. This is evident in the 11 cases that received CAM treatment alone following surgical removal of tumours and did not require any chemotherapy to achieve a state of remission. Another critical observation in this case series that may support the argument above can be seen in the ability of a patient who was planned for palliation. This patient was able to achieve remission and survived from the ovarian cancer using CAM treatment only, without undergoing bowel resection or other function-limiting surgeries, nor receiving any chemotherapy.

The other CAM elements used in the integrative medicine protocol such as the dietary changes and mind and body therapy may also have augmented the treatment process positively [29,30]. Numerous other CAM was used in the protocol, precluding us from discussing each of them in this case series. Nevertheless, the principle of integrative medicine used in the integrative medicine protocol addressed not only the biological but also the psychological, social and spiritual aspects of health and illness. This may have resulted in more holistic treatment for the patients and improved overall health status thus, healing from the disease.

Some of the CAM used in the integrative medicine protocol are deemed controversial and are not recommended for use either as nutritional supplements or as a treatment in the current mainstream medicine. However, promising new findings on the controversial CAM usage in cancer treatment are emerging in the scientific literature. The mechanism and advantageous effects of some of these CAM to the human immune system, psychology, and mental health have been researched and published. Based on these scientific findings, the CAM was carefully selected to be used in the integrative medicine protocol for the treatment of ovarian cancers in the medical centre.

The treatment and management of advanced and recurrent ovarian cancers are exceedingly challenging, as the current treatment modalities only infrequently lead to long-term remission or favourable outcomes. The positive findings from CAM use as found in this case series represent a breakthrough and offer hope to improve cancer treatment and outcomes for some patients with advanced and recurrent ovarian cancers. Undeniably, modern surgery, chemotherapy, and radiotherapy are indispensable modalities in the arsenal of cancer treatment, and CAM should not be promoted or used to replace those completely. Both conventional therapies and CAM should be considered to be used together, or as an adjunct therapy to each other, for the treatment of advanced cancers in a holistic approach, and in this context, advanced and recurrent ovarian cancers.

This case series is not without any limitations. It lacked a comparison group and is limited by its retrospective and observational nature. Selection bias also could not be eliminated due to the nature of the study design. Data that enable us to evaluate specific, measurable clinical effects, complications, safety issues or side effects of the CAM were also not extracted during the write up of this case series. Despite that, the findings of this case series are relevant and undoubtedly useful for generating future study hypotheses on integrative medicine for advanced and recurrent ovarian cancer.

Future studies should uncover and understand the views of medical practitioners and patients' perspective on integrative medicine as a possible treatment approach. We also recommend that appropriately designed clinical trials with a focus on specific clusters of cancers, be initiated to evaluate the overall effects of integrative medicine on patient's survival and quality of life. To complement that, current research that evaluates the science of well-researched and promising CAM compounds or methods should be further expanded for innovation and integration into modern medicine. It is rightful to offer patients with cancers a more personalized and holistic treatment strategy, especially for those with advanced age and disease stage where treatment is more than often challenging.

5. Conclusion

Integrative medicine in cancers is an underutilised practice, and it is a novel field that has yet to be fully explored. This case series, albeit a small retrospective study, certainly offers some insights to what integrative medicine may offer for patients diagnosed with advanced and recurrent ovarian cancers. Unquestionably, more studies must be done to evaluate the efficacy, creditability, and opportunities of CAM treatment. However, its use in conjunction with conventional treatment as a new therapeutic perspective, must be given due attention considering that many women may benefit from its use. Therefore, we suggest that the integrative approach be given due consideration for future research and application in advanced cancers. More importantly, controversial elements used in CAM should not be abandoned without rediscovering their potentials for treatment in modern medicine.

Ethics approval and consent to participate

This case series does not contain any direct studies with human or animal subjects performed by any of the authors. The case series is based on retrospective data from medical records. The case series was conducted and written in compliance with ethical principles outlined in the Declaration of Helsinki and Malaysian Good Clinical Practice (GCP) Guidelines. All data analysed in this case series was anonymised and kept confidential as per applicable laws and regulations in Malaysia. This case series obtained publication approval from Director General of Health, Ministry of Health, Malaysia (KKM.NIHSEC.800–4/4/1 Jld.64(13)) (National Medical Research Register, Malaysia, Identification number; NMRR-18-3552-44982).

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this case series are not publicly available due to data sharing restrictions policy of the study.

Conflicts of interest

SLL, AHSS, and WYL declared that they have no competing interests. VJS is the owner of Dr Vijae Integrative Cancer Center, where the integrative medicine protocol is being delivered.

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Authors' contribution

Study conception and design: VJ, AHS, Acquisition of data and verification: VJ, Analysis and interpretation of data: SLL, VJ, WYL, Drafting of the manuscript: VJ, AHS, SLL, Critical manuscript revision: VJ, SLL, AHS, WYL.

All authors revised the article and approved the final publication and are accountable for the final paper.

Disclosure

The views, interpretations, implications, conclusions and recommendations expressed in this paper are those of the authors alone.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctcp.2019.09.001.

Appendix 1 CAM modalities and list of therapies

A. Complementary and alternative medicine modalities used in integrative medicine protocol

Each patient underwent and received the combinations of the following six (6) facets of integrative therapy for advanced and recurrent ovarian cancers treatment.

a) Specific Anti-Cancer Treatment
   i. High dose vitamin C (sodium ascorbate)
   ii. Vitamin D optimisation
   iii. High dose EPA/DHA (eicosapentaenoic acid/docosahexaenoic acid)
   iv. Melatonin
   v. Oxygenation and alkalinisation
   vi. Amygdalin
   vii. Micronutrient supplementation (including but not limited to selenium and magnesium)
b) Modulation of the Immune System Therapy
   i. Bowel rehabilitation
   ii. High dose vitamin C
   iii. Dietary modifications (see no. d)
   iv. Mistletoe therapy
c) Detoxification and Optimisation of Metabolic Function Therapy
   i. Bowel rehabilitation and micro-biome restoration
   ii. Infrared saunas
   iii. Breathing exercises
   iv. Lifestyle changes (see no. e)
d) Nutritional Counselling

Each patient underwent a full 3-hour session with a nutritionist to learn the concept of healthy eating and the impact of cellular nutrition. This was further reinforced through interaction with a chef that taught food preparation, to allow a smooth transition to a healthy diet focusing on cellular nutrition.

e) Lifestyle Modifications

Lifestyle modifications were advocated in each of the patients. The modification included encouragement to attain adequate physical exercise, performing meditation and similar activities such as Taichi and Qigong, grounding, practising healthy sleep rhythms and minimising electromagnetic field exposure from various sources. Maintaining an active social life and cultivating hobbies were encouraged in the lifestyle modification module.

f) Psycho-Neuroendocrine Immunology Therapy (PNEI)

PNEI is a mind-body therapy that also acted as a non-pharmacologic adjunct treatment option. Each patient received this therapy to enhance their cellular immunity and promote optimal wellness.

B. List of nutritional and metabolic therapy used as CAM in the integrative medicine protocol

Intravenous therapy	Oral therapy
Ascorbic acid 3 gm/500 mg	Vitamin B complex: Thiamine 100 mg
Vitamin B17 3 gm in 10 ml	Riboflavin 75 mg
Magnesium sulphate 2.47 gm in 5 ml	Niacin 100 mg
Anti-oxidant support: Gluthathione 5000 mg	Pyridoxine HCI 100 mg
Alpha lipoic acid 200 mg	Folate 400mcg
Vitamin E 300 mg	Methylcobalamin 300mcg
Pro vitamin B3 250 mg	Biotin 1000mcg
Pro vitamin B5 100 mg	Pantothenic acid 500 mg
Collagen 350 mg	Inositol 100 mg
Ascorbic acid 1500 mg	Para-aminobenzoic acid 50 mg
Vitamin B complex: Thiamine 250 mg	Omega 3: Eicosapentaenoic acid 700 mg
Riboflavin 4 mg	Docosahexaenoic acid 500 mg
Pyridoxine 50 mg	Docosapentaenoic acid 50 mg
D-penthanol 5 mg	Polyphen oil 300 mg
Nicotinamide 160 mg	Sesame seed lignan extract 10 mg
Mistletoe extracts: Helixor M 100 mg in 2 ml	Enzymes: Protease SP 25,000 FCC (HUT)
	Bromelain 800,000 FCC (PU)
	Amylase 10,000 FCC (DU)
	Cellulase 2000 RFF (ALU)
	Lipase 7500 FCC (FIP)
	Anti-oxidants: Vitamin C 500 mg
	L-glutathione 50 mg
	L-cysteine hydrochloride 200 mg
	Biotin 2500mcg
	Alpha-Lipoic Acid 250 mg
	Vitamin C 1000 mg with dihydroquercetin 10 mg
	Selenium complex 200 mcg with vitamin E 20.1 mg
	Others: Black cumin seed oil 500 mg
	Curcumin 400 mg
	Taurine 100 mg
	Zinc caps 50 mg
	Vitamin D3 5000 IU
	Vitamin D3 7000IU
	S-Adenosyl-Methionine 400 mg
	N-Acetyl-L-cysteine 600 mg
	Magnesium 500 mg
	Se-Methyl L-selenocysteine 200 mcg
	Melatonin 3 mg, 10 mg, 50 mg

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