Majority of gynaecological oncologists face this question regularly, but lack of evidence based clinical recommendations in such situations is the main reason why these patients still receive aggressive chemotherapy at the end of their lives.

Decision making about discontinuation of treatment involves patient expectations, physician knowledge and attitude, and scientific evidence concerning treatment. Before continuation of treatment of recurrent or resistant ovarian cancer it is critically important that clinicians not only consider the opportunity to achieve an objective response when selecting a specific second-line treatment strategy, but also how treatment will affect the women’s quality of life. Currently the decision of stopping chemotherapy is made only when the doctor feels that this mode of treatment will not benefit for patient and starting of palliative care will provide relief of symptoms instead of chemotherapeutic drug induced toxicities.

Treatment of recurrent ovarian cancer has more as prolongation of survival than curative role. In this patient setting quality of life and control of symptoms should become the main objectives of treatment.

Patients who receive aggressive care do not have improvement in survival, but they have more hospitalization episodes and patients who progress are more likely to receive therapy shortly before death (1). Furthermore, patients with a shorter survival time have a trend toward increased chemotherapy during their last 3 months of life and have increased overall aggressiveness of care (2).

Adverse disease prognostic factors which include poor performance status, peritoneal carcinomatosis, platinum refractory and resistant disease, residual disease after surgery, advanced stage at initial diagnosis, tumor differentiation, ascites, tumor histology, age and others cannot precisely anticipate when particular patient will survive for 5 years and when only for some months. To predict major adverse disease outcome, optimal time for discontinuation of specific treatment and time for switching to the palliative care should be assessed by several predictors who could predict death within 3-6 months.

In the United States and Canada admission criteria for government-funded hospices or certain regional palliative care programs require physicians to identify those patients with life expectancies of 6 months or less. Report from the National Hospice Organization in 1993 showed that more than 50% of patients with terminal cancer were not given access to hospice services or were referred too late in the course of their illness to take full advantage of the support provided by hospice programs (3-6). Overly optimistic survival predictions made by different health care providers have affected patient referrals to hospice programs adversely (3). On the other hand, premature referral to hospices or palliative care programs may create organizational, financial, clinical, and emotional problems for administrators, health care providers, and patients (7).

Prognostic factors that have been proven as adverse prognosticators are separately discussed below.

**Poor Performance Status or Inoperable Tumors of Upper Abdominal Cavity and Mesentery**

Winter et al. has suggested that patients with ECOG (Eastern Cooperative Oncology Group) performance status 0 have better prognosis than patients with performance status 1-2 (8).

In a study of Omura et al. performance status at time of first-line treatment (0 vs. 1-2; P = 0.013) and performance status at time of second-line treatment (0 vs. 1-2; P = 0.004) were found to be independent significant factors for overall survival whereas age (younger than 65 years vs. older than 65 years) yielded no independent information (9).

In two other case series performance status was no longer a significant predictor of survival in the presence of laboratory variables such as low serum albumin level (10, 11).

Association between performance status and survival may vary with length of follow-up (12, 13). Moreover, performance status is a subjective rating that may be markedly influenced by acute but self-limited events. Performance status of 0 or 1 in a relatively asymptomatic patient may temporarily drop to a performance status of 3 or 4 resulting from the occurrence of acute infectious illnesses.

Most would agree that patients with extreme tumor burdens, such as bulky carcinomatosis should not be considered for surgery, but patients with relatively limited tumor burdens are candidates for surgery. Although the meaning “inoperability” differs across the centers. In the case of bulky disease to obtain resectability some centers would advise neoadjuvant chemotherapy, but study designs of largest trials are doubtful and have been translated differently.

In the study of Alison et al. disease findings which most often precluded optimal debulking were diseases involving the base of the mesentery (94%), confluent diaphragmatic disease (74%), and large volume, confluent peritoneal disease (50%). Besides, more than 50% of gynaecological
oncologists would never perform resection of diaphragmatic disease, resection of parenchymal liver metastases, or ablation with cavitron ultrasonic surgical aspirator or argon beam (14).

**Platinum Refractory or Resistant Ovarian Cancer**

Patients with disease recurrence or progression within 6 months from initial treatment are treated with a number of second-line agents, with response rates of 12 to 30% with a 9-month median survival (15-18). These patients are in a high risk group for disease progression and limited survival.

European Society of Medical Oncologists statement proposes since the achievement of durable response is rare and cure almost impossible, the main goal of salvage therapy in this group of patients is palliation; therefore, particular attention should be paid to the side-effects of the drugs used.

Proceeding the statement, palliative secondary surgery should be considered to relieve intestinal obstruction in patients who have failed two or more chemotherapy regimens. The criteria for selection of patients for palliative surgery are categorized according to the presumptive estimate of duration of survival, the overall medical status and performance status, presence of ascites, the will to live, presence of focal disease and a suspicion of local obstruction where a bypass or local resection might be feasible (19).

**Recurrent Ovarian Cancer and Surgical Cytoreduction**

Optimal cytoreduction is thought as one of the most important prognostic factors. Those who experience disease recurrence and have platinum sensitive tumors are candidates for secondary and tertiary cytoreductive surgery. But there are still a small proportion of patients who will survive for 5 years even if they have been suboptimally cytoreduced. In the study of Chi et al. 87 patients with stage III disease with greater than 2 cm of residual disease had a 5-year survival rate of 21% (20). In this aspect suboptimal cytoreduction separately cannot be used when deciding for palliative care, although chemotherapy applied for these patients will not cure them.

Optimal cytoreduction in platinum sensitive patients can be repeated and has a great value in long term survival. In the patient setting who underwent cytoreductive surgery for the third time median overall survival was 37.8 months for patients without residual tumor; versus 19.0 months for residual tumor ≤ 1 cm and 6.9 months for residual tumor > 1 cm (P < 0.001). Median for overall survival of 6.9 months had a range of 3.05-10.7 months which implies that even in patients with suboptimal cytoreduction other adverse predictive factors should be accounted before discontinuation of specific therapy (21, 22).

**Ascites, Weight Loss, Low Albumins and Lymphocytes and Other Adverse Prognostic Factors**

In multivariate analysis ascites > 500 ml has been considered as adverse prognostic factor indicating short overall survival, but similarly as with the other adverse prognosticators this should be assessed in context with other prognostic factors, because accumulation of ascites can be eradicated when optimal cytoreduction without residual tumor is achieved. Besides, treatment for ascites and intraabdominal dissemination in future potentially might be improved with upcoming chemotherapy agents – bevacizumab and catumaxumab (23).

In 2003 Gruenigen et al. reported that there is linear increase in hospitalization for ascites around 6 months preceding death (24).

The independent prognostic values of weight loss, low lymphocyte counts, and low serum albumin levels are attributable to the role of malnutrition in survival of patients with terminal cancer (25).

Survival in patients with shorter prognoses (<2 months) is associated with the decrease in serum albumin level, but for terminally ill patients with cancer who survive longer than 2 months, the prognosis appears to be more correlated with other consequences of malnutrition such as the impairment in the immune system and the decrease in body weight (26).

Other adverse predictors of survival like severe or modest co-morbidity, elevated preoperative serum platelet counts, lower serum hemoglobin concentrations, elevated serum lactate dehydrogenase, clear cell and mucinous histology and tumor grade should always be evaluated in context with other risk factors that might indicate on survival less than 6 months (27-30).

**Pleural, Parenchymal and Distant Metastases**

Discontinuation of specific treatment for patients with pleural, parenchymal or distant metastases should be appraised if metastases are not surgically resectable.

Apparent liver metastases could be suggestive to physician when to start considering about palliative care. There are approximately 20 months from the diagnosis to develop distant metastases in patients with advanced ovarian cancer and median survival from the diagnosis of parenchymal liver metastasis is 10 months (31).

Five-year survival rates for patients who meet the prerequisites for pulmonary resection ranges from 17 to 36%. This is a substantial improvement over the historical rate of 6% when surgical resection was not used (32).

Patients with brain metastases are another category for whom palliative therapy should be considered. The current evidence indicates that the development of brain metastasis has a poor prognosis, with less than a 9-month survival. With no treatment, survival has been reported to be approximately 0.5–2 months (33, 34).

**Bowel Obstruction**

Patients with multiple sites of intestinal obstruction and those with rapidly progressive disease are not good candidates for surgery; therefore surgery should not be routinely undertaken in these patients. Surgery should be applied for selected patients with mechanical obstruction and/or limited tumor,
single site of obstruction, and those with a reasonable chance of further response to antineoplastic therapy (35).

In the study of Jong et al. benefit of palliative surgery for bowel obstruction in advanced ovarian cancer was associated with the absence of four prognostic factors: palpable abdominal and pelvic masses, ascites exceeding 3 L, multiple obstructive sites and preoperative weight loss greater than 9 kg (36).

It is assumed that benefit from surgery is defined as at least 60 days of survival after the operation. However, the assessment of quality of life, re-obstructions, symptom control, and patient overall comfort, has not been considered in most publications.

In advanced cancer patients, surgical palliation is a complex issue. The decision to proceed with surgery must be carefully evaluated for each individual patient. In patients with advanced ovarian cancer and no or minimal chance of response to antineoplastic treatment, operative interventions must be carefully weighted in light of the limited survival, prolonged hospitalization, high morbidity and mortality, and potential failure to resolve the obstruction.

Symptoms can be palliated in close to 90% of patients by using surgical and nonsurgical procedures, but patients who have surgical palliation have prolonged median survival (191 vs. 78 days) when compared to endoscopic procedures. Approximately half of the patients will have recurrence of their symptoms within 3 months of the procedure (37).

Prognostic indicators published by Ripamonti et al. of low likelihood of clinical benefit from surgery for malignant bowel obstruction (38):

1. Obstruction secondary to cancer;
2. Intestinal motility problems due to diffuse intraperitoneal carcinomatosis;
3. Widespread tumor;
4. Patients over 65 in association with cachexia;
5. Ascites requiring frequent paracentesis;
6. Low serum albumin level and low serum prealbumin level;
7. Previous radiotherapy of the abdomen or pelvis;
8. Patients with nutritional deficits;
9. Diffuse palpable intra-abdominal masses and liver involvement;
10. Distant metastases, pleural effusion or pulmonary metastases;
11. Multiple partial bowel obstruction with prolonged passage time on radiograph examination;
12. Elevated blood urea nitrogen levels, elevated alkaline phosphatase levels, advanced tumor stage, short diagnosis to obstruction interval;
13. Poor performance status;
14. A recent laparotomy which demonstrated that further corrective surgery was not possible;
15. Previous abdominal surgery which showed diffuse metastatic cancer;
16. Involvement of proximal stomach;
17. Extra-abdominal metastases producing symptoms which are difficult to control (e.g., dyspnea).

Hospitalizations for bowel obstruction, pleural effusion, and ascites, especially more than one, should be considered one indication that chemotherapy is unlikely to be of significant further use (39). Besides, it has been observed that chemotherapy at the end of live favors additional clinical events. In the study conducted by Gruenigen 43% patients received chemotherapy 4-6 months before death and 83% of patients 3 months before death (40). Those who received chemotherapy had more significant clinical events, although difference was not statistically significant.

**Palliative Care**

Traditionally, palliation means reduction of physical symptoms and not necessarily improvement of emotions. It has been proposed that palliation should encompass physical and also emotional symptoms.

During palliative treatment, the aim is for overall improvement in the person’s well-being.

In the study of Doyle et al. objective response, an improvement in quality of life was observed in a significant proportion of patients who received palliative chemotherapy. After two cycles of chemotherapy, 52% of patients noted an improvement in their global health status/desirability of life subscale of the European Organisation for Research and Treatment of Cancer quality of life questionnaire Core 30 (EORTC C-30), while the global score of the Functional Assessment of Cancer Therapy for Ovarian cancer patients FACT-O) was improved in 43% of women (41). Measures were reassessed by measuring quality of life score after 2 cycles of chemotherapy, because it was thought that patients receiving of more than two cycles can influence these data, but they were confirmed after analysis of patterns of improvement and duration of improvement. It was considered that most of improvements were observed in emotional subscale, therefore other therapeutic options such as placebo or group meetings and talking for improvement of emotional wellbeing should be assessed in this patient setting.

In addition to the emotional aspect, many symptom subscales in this study showed clear improvement in physical symptoms, particularly nausea, vomiting, pain, and loss of appetite (41).

Controversially results of a study published in 2008 by Alexi et al. showed that, patients who did not receive aggressive care in their final weeks had a mean quality of life score of 6.4 out of 10 compared with 4.6 for those who received at least three aggressive therapies (42).

**Cost-Effectiveness of Hospice at the End of Life**

Approximately 25–27% of Medicare expenditures are spent annually on patients during their last 60 days of life. Studies suggest hospice services decrease end-of-life expenditures by 25–40% (43-45).

An analysis of palliative care costs from patients treated at home with end-stage cancer from the Netherlands found a 2/3 reduction in health care costs by transferring end-of-life care from the hospital to the home setting (46).
Lewin et al. demonstrated that there is a significant cost difference with no appreciable improvement in survival between ovarian cancers patients treated aggressively versus on hospice at the end-of-life. Although not significant, patients in the hospice group actually lived longer despite decreased interventions and cost (47).

Aggressive treatment at the end of life is expensive and it is becoming more common. In results published in 2004, Earle et al. found that in 1996 5.7% of patients in the study started a new chemotherapy regimen within 30 days of death compared with 4.9% in 1993 (48).

As recently reported, the mean cost per patient from initiation of second- or third-line chemotherapy until death was estimated to be $53,000 with 45% of this total cost attributable to chemotherapy (49).

**Patient’s Position**

For some patients’ continuation of treatment, regardless of effectiveness, has great meaning and adds value to existence (50). Brown et al. reported that only 5% patients with gynaecological malignancies predicted that they would discontinue their treatment if it was futile (51). The study by Donovan et al. examining treatment preferences using a treatment decision board found that 25% of recently diagnosed ovarian cancer patients indicated that they would never switch to palliative care, but would choose salvage therapy even if the anticipated median survival time was <1 week, but 14% anticipated not choosing salvage chemotherapy following recurrence, preferring palliative care (52).

Patients typically overestimate prognosis, positively reinterpret their prognosis, and confuse “response” with “cure” (53).

**Position of Gynaecological Oncologists**

Ramondetta et al. sought to explore the Society of Gynecological Oncologists members’ opinions and decisions about end-of-life issues and incurable conditions (54). The survey explored opinions, experiences and decisions in managing terminally ill gynaecological oncology patients. Analysis was based on 327 questionnaires that were returned.

Respondents believed that 97% of patients who are dying realize that they are dying, but stated only 40% of these patients initiate conversations about end-of-life issues. In contrast, 92% of respondents stated that they initiate end-of-life discussions with patients. Ninety-two percent of respondents thought that the patients should be allowed to make end-of-life choices independently after the facts are given to them.

However, 44% thought that it is important to influence the way information is presented, and 54% believe that the gynaecologic oncologist controls the outcome of end-of-life discussions and 40% answered that their actions prolong the process of dying. Although the physicians’ sex, race, religion, and age did not correlate with their treatment decisions, religion did correlate with less fear of death (P=0.011) and less discomfort when talking with patients about death (P=0.005). Members of Society of Gynecological Oncologists were asked to rank the most important factors they believed which influence physicians’ recommendations to discontinue treatment. The most frequently cited reasons were patient’s request (69%) and poor quality of life (70%), followed by poor chances of a cure (43%).

Similarly, respondents believed that the most important factors influencing a patient’s decision to discontinue treatment were poor quality of life (78%) and poor chances of a cure (59%). Doctors were asked about frequency with which some palliative procedures are performed. More frequently performed procedures included bowel obstruction surgery for ovarian cancer (59%), repeated tumor debulking (40%), and tumor debulking surgery in patients with liver metastasis 20%.

Respondents younger than 40 years were more likely to report that “very often” or “often” they would perform a debulking of ovarian cancer in the presence of multiple liver metastases than those 40 years or older (33% versus 14%, P<0.001). Respondents with less than 6 years of post-training practice were also more likely to perform this surgical procedure than those with more years of post-training.

**Strategy to Develop an Optimal Management Approach in Recurrent Ovarian Cancer for an Individual Patient is Proposed by Markman (55):**

- Focus on realistic goals for the individual patient at a particular time in the natural history of her own illness;
- Understand (and explain to the patient/family) the concept of ovarian cancer as a very serious but chronic disease process. Thus, for example, it is critical that one considers that a particular treatment delivered today may impact (positive or negative) on a substantial percentage of the remainder of the patient’s life;
- Use all currently available population-based study data (phases 3 and 2 trials, with priority given to information associated with the highest level of evidence);
- Consider patient-centered data (co-morbidity and prior treatment-related experience of this patient);
- Physician’s personal experience with management options in similar patients;
- Open, honest, and thorough discussion with the patient and family regarding realistic goals and expectations of therapy.

It is essential to communicate clearly with patients when deciding on treatment after multiple drugs have failed, as the likelihood of benefit is low, particularly in patients with poor performance status and large volume disease.

When discussing with patient accent should be made also on benefits of palliative care. This is not only discontinuation of treatment. This is active treatment with the purpose to improve patient’s quality of life, which includes assessment and treatment of pain, other physical, psychosocial and spiritual problems.

There is evidence indicating that specific procedures, such as paracentesis and thoracentesis, relieve symptoms more than chemotherapy at the end of life (24).
At the end of life sometimes psychological and spiritual aspects can become more important than physical and in case of palliative care more credibly patient will receive more psychological support from palliative care team.

Payne et al. reported that anxiety and depression accounted for most of the variance in quality of life measurements in breast and ovarian cancer patients receiving palliative chemotherapy (56).

It is possible that for some patients, especially older, quality of life is more important than expectations for their possible live prolongation. Even more, quality of their life still can be more important even in situations where there is evidence based improvement in overall survival, for example, of 2-5 months. Therefore comprehensive discussion on these relevant issues is extremely important before continuation or discontinuation of specific treatment in the presence of adverse prognostic factors.

It is also critical that future randomized trials in this area focus on issues of quality as well as quantity of life.

Conclusion

Doctors should initiate discussion about end-of-life issues and possible switching to palliative therapy when patient’s has got some of adverse prognostic factors when expected survival is approximately 6 months.

**Prognostic factors that could predict short survival:**

- unresectable, bulky tumor in upper abdomen or mesocolon;
- pleural, parenchymal or other distant unresectable metastases;
- platinum refractory or resistant ovarian cancer;
- multiple sites of intestinal obstruction;
- contributing factors like poor performance status, large ascites, elevated serum platelet count, low hemoglobin concentration, low albumin, low total protein, increasing age, clear cell and mucinous histology, high and intermediate tumor grade, DNA aneuploidy etc.

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