Management of Epithelial Ovarian Cancer in Older Patients in the Adam Malik Central Hospital of Medan

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ABSTRACT

Ovarian cancer is the eighth most common cancer in women and is ranked 18th most common cancer in the world. Based on *SEER*, 47% of ovarian cancers occur in women over 65 years of age. Decreased life expectancy in older ovarian cancer patients can be due to: more aggressive cancer cells at old age; resistance of cancer cells to chemotherapy; individual patient factors; inadequate surgery and suboptimal chemotherapy. As many as 75% of women with ovarian cancer are diagnosed at an advanced stage so the prognosis is poor. Consideration of chemotherapy doses, scheduling, route and time, is very important to determine the safest and most effective treatment with consideration of geriatric assessment, such as functional dependence, organ function, comorbidity, polypharmacy, social support, and cognition/ psychosocial factors. The purpose of this study was to determine the characteristics and treatment of ovarian cancer in older patients, especially in H. Adam Malik General Hospital, Medan.

Data about ovarian cancer were obtained from the cancer registry, and through SIRS data (Hospital information system, *Sistem informasi rumah sakit*) with following keywords: ovarian cancer and malignant ovarian tumor corresponding to ICD10. After that, results search were filtered for patients older than 60 years old, and checked one by one to ensure that the patient was diagnosed with ovarian cancer. Then, the characteristics and management of the patient were obtained from the medical record.

This research was conducted at Haji Adam Malik Hospital which is a class A general hospital in Medan as well as a referral hospital of Development Area A which covers the provinces North Sumatra, Nanggroe Aceh Darussalam, West Sumatra, and Riau. Through SIRS data, we found that 132 patients were diagnosed with ovarian cancer and malignant ovarian tumor from 2016-2018. From the cases registered at H Adam Malik General Hospital, only 15 cases were in accordance with screening criteria, namely patients over the age of 60 years. Most patients were aged between 66-70 years (53.33%), histopathologically had the adenocarcinoma mucinous type (33.33%), and most were in stage IIIC (20%). For surgery, we found optimal primary debulking of 53.33%, suboptimal primary debulking of 33.33% and 13,345 primary debulking were not carried out. More patients had ASA scores with a range of 0-1 (53.33%) than patients with ASA scores of 2-3 (33.33%). 5 patients had good outcome (53.33%), 1 patient passed away (33.33%), and there was as much as 53.33% loss of follow-up with unknown outcome. Conclusion: the management of ovarian cancer in older patients in Dr. H. Adam Malik Hospital is in accordance with EBM.

Keywords: Epithelial Ovarian Cancer, Old Age

INTRODUCTION

Ovarian cancer is the eighth most common cancer in women and the 18th most common cancer in the world. In 2018, the number of new ovarian cancer cases reached 295.414 cases and 184.799 deaths.[1,2,3]

According to *SEER (*Surveillance, Epidemiology, and End Results), 47% ovarian cancers occur in women over 65 years of age. This figure is expected to increase in the coming decades. Data in

Europe shows that one-year life expectancy is 57% in women aged 65-69 years, 45% in women aged 70-74 years, and 33% in women aged 80-84 years.[4,5,6]

Decreased life expectancy in elderly ovarian cancer patients is due to: (1) more aggressive cancer cells in older patients; (2) resistance of cancer cells to chemotherapy; (3) individual patient factors, such as other health problems, polypharmacy, functional dependence, cognitive impairment, depression, weakness, lack of nutrition, limited social support; and (4) inadequate surgery and suboptimal chemotherapy.[4,7]

As many as 75% of women with ovarian cancer are diagnosed at an advanced stage (International Federation of Gynecology and Obstetrics [FIGO] IIIC - IV). Patients with stage IIIC - IV (FIGO) cancer have worse prognosis than patients with advanced stage but limited spread.[6,8]

Management of advanced ovarian cancer usually begins with a combination of extensive debulking surgery and adjuvant platinum-based chemotherapy. This approach usually yields improved median survival of over 50 months. However, recent data suggests that elderly patients with ovarian cancer have a worse survival rate compared to younger patients. This is partly due to reduced use of standard chemotherapy. Only a proportion of women aged 65 years receive platinum-based first-line therapy. However, survival increased by 38% in women treated with chemotherapy.[9,10]

Primary chemotherapy along with cytoreduction surgery are potent management modalities. Considerations of chemotherapy, including dose, schedule, route, and time (neoadjuvant or postoperative) are very important to determine the safest and most effective treatment with consideration of geriatric assessments, such as functional dependence, organ function, comorbidity, polypharmacy, social support, and cognition/psychosocial factors.[11]

Based on the description above, we aim to investigate the characteristics and management of ovarian cancer in elderly patients at Adam Malik Hospital, Medan.

METHODOLOGY

Data on ovarian cancer patients were traced through cancer registry, and through SIRS (hospital information system) data with the keyword ovarian cancer, malignant ovarian tumors according to ICD code 10. The search results were filtered with age criteria of older than 60 years. Ovarian cancer diagnosis was confirmed by checking every entry. Data on patient characteristics and management were obtained from medical records.

LITERATURE REVIEW

Based on UN consensus, the cut off of elderly people is determined to be 60+ years. Within the elderly population, further classifications include eldest (usually 80+), centenarian (100+), and super-centenarian (110+).[12]

According to the Law of the Republic of Indonesia Number 13 of 1998 concerning Elderly Welfare, elderly means someone who has reached the age of 60 years and over.[13]

Optimal therapy for advanced epithelial ovarian cancer (AEOC) consists of primary debulking surgery (PDS) followed by platinum-based chemotherapy. Every 10% increase in the percentage of surgical cytoreduction is associated with 5,5 % increase in the average survival.[5]

Based on a retrospective analysis conducted at three cancer centers in the United States, there was not a significant difference in survival in older and younger women. Patients with advanced (65-75 years) and very advanced age (> 75 years) tolerate radical and ultra-radical surgery without increased morbidity and with similar clinical results to those reported in younger patients. Therefore we conclude that cytoreduction bed is safe and feasible in elderly patients.[5]

Elderly patients often do not receive standard chemotherapy compared to younger patients because of multimorbidity,

poor physical or cognitive performance and risk of death. Chemotherapy toxicities that are common in the older age are gastroenterological toxicity, grade 3-4 hematology and grade 3-4 neutropenia. Retrospective analysis showed that low-dose carboplatin/paclitaxel was better tolerated but just as effective as the standard regimen in elderly ovarian cancer patients with AEOC. First-line chemotherapy with carboplatin/paclitaxel versus cisplatin/paclitaxel after cytoreduction surgery for advanced ovarian cancer was tolerated in the older population but the initial discontinuation of therapy was double in patients over the age of 70 compared with younger patients. [5]

Targeted therapy is a specific treatment for cancer cells. This treatment plays a role in inhibiting the molecules in cancer cell growth. Several targeted therapies approved for treatment of ovarian cancer are bevacizumab (Avastin), olaparib (Lynparza), rucaparib (rubraca), and niraparib (zejula). [14]

Bevacizumab is a human vascular endothelial growth factor (VEGF)-neutralizing monoclonal antibody that inhibits tumor angiogenesis. Several phase 3 trials showed that bevacizumab, in combination with chemotherapy, improves Progression Free Survival (PFS) in first line advanced ovarian cancer therapy and also in platinum-sensitive relapse and resistance to platinum, however, clinical trials in older patients are still lacking. [5]

GOG-218 is a phase III randomized trial of the use of bevacizumab with chemotherapy in first-line ovarian cancer, in which bevacizumab prolongs median PFS by about 4 months across all age ranges. OCEANS is a randomized, phase III trial evaluating the addition of biologic therapy to standard chemotherapy in platinum sensitive recurrent ovarian cancer resulting in a statistically significant improvement in PFS among both patients over and under 65 years of age. Bevacizumab is an active and tolerable initial-line treatment option that should be considered regardless of age. [5]

RESULTS

This research was conducted at Haji Adam Malik Hospital located at Jalan Bunga Lau No. 17, Kemenangan Tani Village, Medan Tuntung District. Haji Adam Malik Hospital is a class A General Hospital in Medan in accordance with the Decree of the Minister of Health of the Republic of Indonesia Number: 775/MENKES/SK/IX/1992.

Through SIRS data, 132 patients were diagnosed with ovarian cancer and ovarian tumors from 2016-2018. Of the cases registered at Haji Adam Malk General Hospital, only 15 cases were in accordance with the inclusion criteria of patients aged over 60 years.

Table 1. Distribution of patients based on age

Age (years)	Number of patients (n)	Percentage (%)
61-65	4	26,67
66-70	8	53,33
71-75	0	0,00
76-80	3	20,00
> 80	0	0,00
Total	15	100.0

Based on the table above it can be seen that most patients are aged 66-70 years (53.33 %), with patients only 4 (26.67 %) aged 61-65 years, 3 people (20%) aged 76-80 years, and there are no-one aged 71-75 years and over 80 years.

Table 2. Distribution of patients based on distance from residence to hospital

Distance (km)	Number of patients (n)	Percentage (%)
0-100	8	53,33
101-200	1	6,67
201-300	0	0,00
301-400	2	13,33
401-500	1	6,67
>500	2	13,33
Total	15	100.0

Based on table 2 above, most patients resided within 100 km of Haji Adam Malik Hospital (53.33 %), however 2 patients lived more than 500 km (13.33 %) from the hospital, outside the North Sumatra province.

Table 3. Distribution of patients based on year of diagnosis

Year	Number of patients (n)	Percentage (%)
2016	4	26,67
2017	7	46,66
2018	4	26,67
Total	15	100.0

Based on table 3. it appears that most patients were diagnosed in 2017 (46.66%) in this study. Meanwhile, throughout 2018 only 4 (26,67%) was diagnosed with ovarian cancer. In addition, there were also patients diagnosed in 2016 (26,67 %).

Table 4. Distribution of patients based on histopathology results

Histopathology type	Number of patients (n)	Percentage (%)
Keratinizing squamous cell carcinoma	1	6,67
Clear cell adeno ca ovari	2	13,33
Moderately differentiated adeno carcinoma	2	13,33
Mucinous adeno ca ovarium	5	33,33
Metastase granulosa cell tumor	2	13,33
Mucinous ovarii	1	6,67
Endometrioid adeno ca moderate diff	1	6,67
Bilteral moderately differentiated adeno Ca of ovaries	1	6,67
Total	15	100.0

Based on table 4 above, it can be seen that histopathologically, more patients had mucinous adenoic ovary type cancer (33.33 %).

Table 5. Distribution of patients based on stage

Stage	Number of patients (n)	Percentage (%)
I A	2	13,33
I C1	1	6,67
I C3	1	6,67
II B	1	6,67
III C	3	20,00
Unknown	7	46,67
Total	15	100.0

Based on table 5 above, most patients were diagnosed at stage IIIC (20%) followed by stage IA (13.33%), and unknown in as much as 46.67% patients.

Table 6. Distribution of patient based on primary debulking

Primary debulking	Number of patients (n)	Percentage (%)
Suboptimal	5	33,33
Optimal	8	53,33
None	2	13,34
Total	15	100.0

Based on table 6 above, it appears that more patients underwent optimal debulking surgery

Table 7. Distribution of patients based on ASA score

ASA	Number of patients (n)	Percentage (%)
0-1	8	53,33
2-3	5	33,33
Loss follow up	2	13,34
Total	15	100.0

Based on table 7 above, more patients had ASA score with a range of 0-1 (53.33%) compared to patients with ASA score of 2-3 (33.33%). ASA score is a classification used to assess the state of the patient prior to surgery. ASA 1 means normal and healthy patients, ASA II means patients with mild to moderate systemic disease, ASA III means patients non-life threatening systemic disease, and ASA IV means patients with life-threatening systemic disease, ASA V means dying patients that may not survive in 24 hours with or without surgery. The last category includes previously healthy patients with uncontrolled bleeding and elderly patients with terminal disease.

Table 8. Distribution of patients based on neoadjuvant chemotherapy

NAC (Neoadjuvant Chemoteraphy)	Number of patients (n)	Percentage (%)
Yes	3	20,00
No	12	80,00
Total	15	100.0

Based on table 8 above, 80% patients did not receive NAC. The NAC given is Carboplatin Paclitaxel.

Table 9. Distribution of patients based on outcome

ASA	Number of patients (n)	Percentage (%)
Alive	5	33,33
Living with Disease (Kanker)	1	6,67
Died	1	6,67
Loss follow up	8	53,33
Total	15	100.0

Based on table 10 above, 5 people were healthy at the end of the data collection (53.33%), whereas 1 patient dies (33.33%). The drawback here is the large percentage of patients with loss of follow-up (53.33) with unknown outcome.

DISCUSSION

The annual incidence of ovarian cancer amounts to 204,000 cases per year

and causes 125,000 deaths. Ovarian cancer patients older than 60 years need to be considered, as elderly women are more likely to have multiple comorbidities with usually higher stage of tumor at discovery. [6]

As Freyer et al (2013) has postulated, various levels of toxicity associated with chemotherapy encountered in elderly patients, among others, are thrombocytopenia ($<50 \times 10^9$/L), neutropenia, febrile neutropenia, anemia, alopecia, neuropathy and still many more.[10]

We found that more patients were diagnosed with ovarian cancer in the range of 61-75 years compared to > 75 years. This was in line with a research by Fanfani et al. (2012) in which the average age of ovarian cancer patients was 65-75 years, also similar to results obtained by Wright et al. (2015) in which the average age of sample in the research was 70-74 years.[9]

Histopathologically, we also found many types of cancer cells in patients with ovarian cancer. In our study, mucinous types were much more commonly found compared to other types. This was not in line with Wright et al. (2015) who found more patients with serous type histopathology.[7]

Many patients had ASA score within range of 0-1 compared to patients with ASA score 2-3. This was in line with research by Fanfani et al. (2012) which found a lot of patients with ASA score of 1-2 compared to ASA score 3-4. Freyer et al. (2013) in their study also found more patients with ASA score of 0-1 compared to patients with a score of 2-3.[6,10]

In our study, more patients underwent primary debulking surgery than not, with a large part having ASA score of 0-1. Marchetti et al., however, found more patients with ovarian cancer aged over 65 years had high ASA score (89% with ASA 3-5) and longer hospitalization compared to younger patients.[15]

More patients did not receive therapy NAC compared to those who did (20%). This was comparable with the research conducted by Fanfani (2012), with only 47.5% patients in age group of 65-75 years receiving NAC. Wright et al (2015) also found in his research that 29.52% patients received NAC while 70.48% only received primary surgery.[6,8]

Wright et al (2015) postulated that use of surgery as therapy modality for ovarian cancer has declined since 1991 through 2007, from 63.2% to 49.5%, while neoadjuvant chemotherapy usage increased from 19.7% to 31.8% in the same years. The findings of the study have not been able to conclude whether debulking primary or neoadjuvant was much better for elderly patients, as it was a descriptive study intending to see the patterns and characteristics of the disease course. Other studies show a decrease in morbidity with neoadjuvant chemotherapy without reducing the survival rate. In continental Europe, neoadjuvant chemotherapy is used in nearly half of patients with advanced disease. Wright et al (2015) showed that neoadjuvant chemotherapy may be a good choice of treatment in elderly patients with ovarian cancer.[8]

There were 5 patients with disease-free survival outcome (53.33%), with only 1 patient dying (33.33%). However, there were a number of patients with loss of follow-up, hence our inability to predict outcome. Fanfani (2012) concluded that more patients had disease-free survival compared to the patients who died.[6]

Validated inclusion criteria on therapies appropriate for patients with advanced age is not yet available. In systematic review focusing on primary debulking surgery on advance age ovarian cancer patients, 30 days mortality varying between 0 to 5.9% with a median of 2.7% has been reported by Gerestein et al. Although the age in the study were not specific, the outcome of death was a little higher in older patients (increased from 5.4 to 11.7%) after surgery. In addition, recently Thrall et al. found that within 30 days the mortality reached 5.6% for elective surgery in elderly patients with ovarian cancer.[16,17]

One study on the tolerance of chemotherapy in 148 elderly oncological patients averaging 73 years old (70 to 84 years) evaluated women with malignancies treated between 1990 and 2000 in four centers, with nearly 70% of participants having ovarian cancer. Comorbidity was found in nearly 80% of patients who received first-line chemotherapy, 96 (64.9%) receiving platinum-based therapy without taxane, 42 (28.4%) receiving platinum/paclitaxel combined therapy, and 10 (6, 8%) receiving a taxane based regimen without platinum. The results showed that there was no significant difference observed in performance before, during, and at the time of completion of fist-line chemotherapy. Grade 3/4 haematological toxicity was reported in 38.2% of the patients, and 6.8% of them discontinued treatment because of toxicity. They conclude there was no significant relationship between comorbidities and toxicity. Furthermore, this research confirmed an earlier report which showed that elderly patients with normal kidney and liver function were better able to tolerate the chemotherapy regimen with similar toxicity profile and that there was no significant differences in delay or discontinuation of treatment.[18,19]

CONCLUSION

Management of elderly ovarian cancer patients in H. Adam Malik Hospital, Medan, consists of primary debulking surgery and neoadjuvant chemotherapy, with more patients receiving only the first modality compared to the latter. This is in accordance with evidence-based medicine.

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