Neo-adjuvant Chemotherapy in Malignant Ovarian Germ Cell Tumor

Pabitra Maharjan[1], Poonam Lama[1], Anisha Shrestha[1], Onika Karki[1], Simit Sapkota[2], Subhas Pandit[2], Suresh Shrestha[2], Sameer Neupane[3], Srijana Koirala[3], Bandana Parajuli[3], Rabindra Desar[4], Jitendra Pariyar[1]

[1]Department of Gynecologic Oncology, Civil Service Hospital, Minbhawan, Kathmandu, Nepal.
[2]Department of Clinical Oncology, Civil Service Hospital, Minbhawan, Kathmandu, Nepal.
[3]Department of Pathology, Civil Service Hospital, Minbhawan, Kathmandu, Nepal.
[4]Department of Radiology, Civil Service hospital, Minbhawan, Kathmandu, Nepal.

Abstract

Introduction: Malignant ovarian germ cell tumors (MOGCT) are common in young females, management of which is associated with fertility and reproductive concerns. Being highly chemo-sensitive, neo-adjuvant chemotherapy (NACT) prior to definitive surgery could help reduce disease burden and increase the possibility of organ preservation.

Methods: A descriptive study was done on ovarian cancer patients with fertility concerns attending Civil Service Hospital of Nepal from 2015 to 2021. Clinical data were collected from hospital registry and telephonic inquiries followed by in-person interviews in all the participants regarding their treatment, present status, oncologic and fertility outcome.

Results: Eighteen MOGCT fertility needs were identified, among which seven underwent NACT (39%) with fertility preserving surgery and were enrolled in the study. Mean age was 16.8 years (range: 15- 19 years). Histologically, of total seven cases, three (43%) were Dysgerminoma in stage IC, three (43%) were yolk sac tumor (2 in stage IC and 1 in stage IIIC), and one (14%) were of mixed germ cell tumor at stage IIIC. All 7 patients underwent fertility preserving surgery after NACT. At the time of presentation, three were married and four were unmarried. Two (28%) patients had recurrence as they defaulted during treatment among which one patient died and the other came after 1 year and completed chemotherapy. Thus 85% (six in seven) of the cases are in complete remission, among which three conceived and had successful delivery.

Conclusion: The present study supports NACT to be beneficial in offering fertility sparing surgery even in advanced stage MOGCT.

Keywords: Malignant ovarian germ cell tumors, Neo-adjuvant chemotherapy

Introduction

Malignant Ovarian Germ Cell Tumors (MOGCTs) are rare tumors that account for 2% - 3% of all ovarian cancers. Being highly chemo-sensitive, fertility sparing surgery, whenever feasible with or without adjuvant chemotherapy, is the standard treatment approach in these patients.[1] MOGCTs can occur in all age groups, with peak incidence in young girls aged from 15 to 19 years old.

The five-year survival rates have reached up to 85% and even more, which is much higher than that of epithelial ovarian cancer. The main reason is the high effectiveness of platinum-based chemotherapy.[2] MOGCT historically carried a poor prognosis, especially among those diagnosed with advanced disease. With the advent of combination chemotherapy, the risk of relapse has markedly decreased. The development of modern surgical staging and effective chemotherapy regimens has markedly improved the outcome of treatment of ovarian germ cell tumors.[3] The fertility preservation approach at the time of surgery and avoidance of

Correspondence: Prof. Dr. Jitendra Pariyar, Gynecologic Oncology Unit, Civil Service hospital, Kathmandu, Nepal.
Email: jipariyar@yahoomail.com

toxicity with systemic chemotherapy play a crucial role in the treatment of MOGCT.

For many years, primary tumor reductive surgery (pTRS) followed by platinum-based adjuvant chemotherapy has been the standard treatment for women with advanced disease. However, neo-adjuvant chemotherapy (NACT) has gradually become an accepted alternative for certain patients for first-line treatment. The rate of NACT use has increased from 8.6% to 22.6% between 2004 and 2013 and from 17.6% to 45.1% between 2006 and 2016 for advanced ovarian cancer. The use of NACT has increased annually by 10.3% between 2011 and 2016 compared with an annual increase of 7.9% between 2006 and 2011.[4]

Methodology:

This is a single institutional retrospective study of seven patients of malignant ovarian germ cell tumor, who had neo-adjuvant chemotherapy for two to three cycles with BEP (bleomycin, etoposide and cisplatin) followed by fertility sparing surgery (unilateral salpingo-oophorectomy + omentectomy ± lymphadenectomy) then again followed by completion of remaining chemotherapy cycles. The cases were registered and treated in the Obstetrics and Gynecology Department of Civil Service Hospital from the year 2015 to 2021 were included in the study. Clinical information about the tumor type, FIGO stage and grade of the tumor, course of neo-adjuvant chemotherapy regimen, surgical procedure and adjuvant chemotherapy courses were collected and recorded from medical records and hospital cancer registry. Follow up data of survival length and of oncologic, menstrual and fertility outcomes were acquired by telephonic inquiry and in-person interview. Reproductive and obstetrical outcomes were also noted. Progression free survival and overall survival (OS) evaluated as clinical outcomes.

Results

Among the total 18 patients of malignant ovarian germ cell tumour, seven (39%) patients who received NACT with fertility-sparing treatment were included. The age range was 15 – 19 years, with the mean age of 16.8 years. All were diagnosed by histopathology examination, except one case of dysgerminoma which was diagnosed by cytology. Among the three histological types of MOGCT, dysgerminoma and yolk sac tumor were noted in three (43%) each and mixed germ cell tumor in one (14%). Most of the patients (72%) among which three dysgerminomas and two yolk sac tumours presented in FIGO stage IC, two patients (28%), one each of yolk sac tumour and mixed germ cell tumour presented in FIGO stage IIIC (Table 1).

Follow up of the last six years showed that two patients (28%), one yolk sac tumor and the other of dysgerminoma, both having FIGO stage IC suffered from relapse (Table 4). In the yolk sac tumor, recurrence was noted to after one year after completion of treatment with fertility sparing surgery and adjuvant chemotherapy. The patient underwent completion surgery: total abdominal hysterectomy with unilateral-salphingo-oophorectomy with para-aortic lymphadenectomy. Unfortunately, the patient defaulted and passed away, with OS of 34 months. The other patient of dysgerminoma had chemotherapy for the salvage treatment, with OS of 68 months. In both patients, the disease-free survival was for twelve months.

All seven patients were nulliparous at disease presentation, although three were married and one married during the remission period. During remission period three patients became pregnant; all had spontaneous conception and had normal progression of pregnancy and delivered healthy babies (Table 5). Two of these patients, 16 and 18years of age, had dysgerminoma at stage IC. The gap between treatment completion and pregnancy was two years. In the other 18 years old patient of mixed germ cell tumor stage IIIC, the gap between treatment completion and pregnancy was six years. Following NACT all patients had responded. Currently, six out of seven patients are alive and disease-free at a median follow-up of 41 months. Six (85%) of patients had no menstrual issue; remaining one (14%) of the patients regained normal menses within six months of completing chemotherapy.

Table 1: Characteristics of patients with MOGCTs treated with NACT and Fertility Sparing Surgery (FSS):

Mean age, years (range)	16.8 years (range: 15–19 years)
Previous Parity • Nullipara • Multipara	 7 0
FIGO Stage • IC • IIIC	 5 (72%) 2 (28%)

Table 2: Treatment of MOGCT with Fertility Preservation:

Oncological Treatment	Frequency	Percentage
Fertility Sparing Surgery (FSS) only	4	22
FSS and Adjuvant Chemotherapy	7	39
NACT, FSS and Adjuvant Chemotherapy	7	39

Table 3: Histologic Type

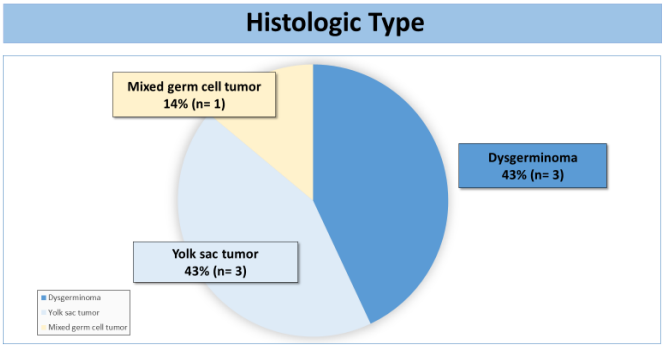

Table 4: Oncologic Outcomes

Complete Remission: 5 (72%)				
Age (years)	**Histology**	**Stage**	**Status**	**Overall Survival (months)**
18	Dysgerminoma	IC	On Remission	36
19	Dysgerminoma	IC	On Remission	60
15	Yolk sac tumor	IIIC	On Remission	36
16	Yolk sac tumor	IC	On Remission	44
17	Mixed germ cell tumor	IIIC	On Remission	36

Recurrence: 2 (28%)						
Age (yrs)	**Histology**	**Stage**	**DFS**	**Salvage tzherapy**	**Status**	**OS (months)**
17	Yolk sac tumor	IC	12	Completion Surgery	DOD	34
16	Dysgerminoma	IC	12	Chemotherapy	NED	43

Discussion

Malignant ovarian germ cell tumors are rare tumors due to which there is limited published literature regarding the clinical profile and outcome of these tumours.[5] The present study had 18 patients of MOGCT among which seven patients underwent NACT followed by surgery and adjuvant chemotherapy. MOGCT is primarily a malignant neoplasm of adolescents and young adults. The median age of the study population reported is around 18-20 years in most studies. [1,6,7] This figure closely paralleled our finding with the mean age of 16.8 years (Table 1).

Dysgerminoma was the common subtype (43%) among the MOGCT, which is comparable to other studies.[5,7] However, immature teratoma and yolk sac tumor were the most common histology in a study done by Ganguly S et al. and Anita et al.[6,8] respectively. One of the studies reported a woman with yolk sac tumor diagnosed at 12 weeks of pregnancy who underwent FSS followed by adjuvant chemotherapy had normal progression of pregnancy and delivered healthy child.[9]

There was no menstrual issue in 85% (n=6) of patients; remaining 15% (n=1) of patient regained normal menses within six months of completing chemotherapy which is consistent with other studies.[10, 8, 11] Park JY et al reported none of the adolescent girls having premature ovarian failure after treatment of MOGCT.[12]

All seven patients responded well following neoadjuvant chemotherapy. Currently, 6 of 7 (85%) patients are alive and disease-free at a median follow-up of 41 months similar to study done by S Talukdar et al.[11] The survival rate was high (100%) in dysgerminoma and mixed type compared to (67%) in yolk sac tumor. Similar findings were also observed

Table 5: Clinical details of patients with Successful Conception and Pregnancy

Age at diagnosis	Diagnosis	Stage	Treatment	Chemotherapy Cycle	Gap between treatment completion and conception	Method of Conception and Pregnancy Outcome
16 years	Dysgerminoma	IC	NACT + FSS + Adjuvant Chemotherapy	4	6 years (72months)	Spontaneous, Healthy baby
18 years	Dysgerminoma	IC	NACT + FSS + Adjuvant Chemotherapy	4	2 years (24months)	Spontaneous, Healthy baby
17 years	Mixed Germ Cell Tumor	IIIC	NACT + FSS + Adjuvant Chemotherapy	6	2 years (24months)	Spontaneous, Healthy baby

in study by Zanetta.G et al.[13] Fertility preserving surgery and adjuvant chemotherapy appear to have little effect on fertility and menstrual cycle with a good overall survival.[8] Neo-adjuvant chemotherapy may not be an easy way out, but is in some patients with stage IIIC or IV ovarian cancer it may be a better alternative treatment option than primary debulking surgery.[14] NACT can also be curative in some of patients with advanced stage malignant ovarian germ cell tumours.[15] NACT also reduces the risk of postoperative mortality, surgical time and the need for stoma particularly in advanced ovarian cancers with bowel involment.[15,16,17] The interval debulking surgery (IDS) group had a statistically significant advantage in median survival time (26 months) compared with the group who had upfront surgery without NACT.[18] In patients of MOGCT treated appropriately with fertility sparing surgery followed by chemotherapy high survival rate up to 100% was reported by Weinberg LE et al.[19] NACT followed by interval fertility sparing conservative surgery may be a reasonable option in patients with extensive disease, when initial debulking is not an option or where the poor general condition or clinical findings suggest an increased risk of surgical morbidity or could pose challenge fertility-sparing retention.[20] In a earlier study many patients opted for radical surgery over conservative surgery due to anxiety of life-threatening disease but in the present study, all desired conservative surgery most likely due to their young age, marital status, menstrual and fertility needs.[21] In the present study, the mean duration of cancer treatment to pregnancy was 40 months which is similar to other study with the mean duration of 42 months from cancer treatment to pregnancy Johansen G.[22]

Conclusions:

The present study supports neoadjuvant chemotherapy to be beneficial in offering fertility sparing surgical option even in advanced stage MOGCT. The oncological and fertility outcomes are highly gratifying as seen in the study. Irrespective of histology and stage, neo-adjuvant chemotherapy followed by surgery could become the standard approach which can result in complete cytoreduction, with high chance of fertility preservation and good menstrual and reproductive outcomes.

References

1. Js A, Sambasivan S, Rema PN, James FV, Krishna J. 621 Neoadjuvant chemotherapy and fertility sparing surgery in advanced malignant germ cell tumor ovary. International Journal of Gynecological Cancer. 2021 Jan 1;31:A257.
2. Uccello M, Boussios S, Samartzis EP, Moschetta M. Systemic anti-cancer treatment in malignant ovarian germ cell tumours (MOGCTs): current management and promising approaches. Ann Transl Med 2020;8(24):1713. DOI: 10.21037/atm.2020.04.15
3. Simone CG, Markham MJ, Dizon DS. Chemotherapy in ovarian germ cell tumors: A systematic review. Gynecol Oncol. 2016 Jun;141(3):602-7. DOI: 10.1016/j.ygyno.2016.02.007. Epub 2016 Feb 9. PMID: 26873864.
4. Patel A, Iyer P, Matsuzaki S, Matsuo K, Sood AK, Fleming ND. Emerging trends in neoadjuvant chemotherapy for ovarian cancer. Cancers. 2021 Feb 5;13(4):626.
5. Topuz S, Iyibozkurt AC, Akhan SE, Keskin N, Yavuz E, Salihoglu Y et al. Malignant germ cell tumors of the ovary: a review of 41 cases and risk factors for recurrence. Eur J Gynaecol Oncol. 2008 Jan 1;29(6):635-7. PMID: 19115694.
6. Ganguly S, Gargy S, Basu A, Chatterjee M, Ghosh A, Chakraborti B, et al. Multidisciplinary management of ovarian germ cell tumours—a single institutional study from India. ecancermedicalscience. 2021 Sep 14; 15:1290. PMID: 34824613, PMCID: PMC8580601. DOI: 10.3332/ecancer.2021.1290
7. Abu-Zaid A, Nazer A, AlOmar O, Azzam A, Al-Eid HS, Elhassan TA, et al. Incidence of malignant ovarian germ cell tumors (MOGCTs) in Saudi Arabia. Hematology/Oncology and Stem Cell Therapy. 2014 Jan 1;7(1):41-3. DOI: 10.1016/j.hemonc.2013.12.001. Epub 2014 Jan 9. PMID: 24412326.
8. Anita AN, Rushdan MN. Reproductive function after treatment of ovarian germ cell malignancy. Med J Malaysia. 2012 Feb;67(1):71-6. PMID: 22582552.

9. Pariyar J, Shrestha B, Rauniyar B, Regmi S, Shrestha J, Jha A, et al. Cancer with pregnancy in a cancer hospital. J. Nepal Health Res. Counc. 2012 Sept; 10 (22) :224-8.

10. Brewer M, Gershenson DM, Herzog CE, Mitchell MF, Silva EG, Wharton JT. Outcome and reproductive function after chemotherapy for ovarian dysgerminoma. J Clin Oncol. 1999 Sep;17(9):2670-75. DOI: 10.1200/JCO.1999.17.9.2670. PMID: 10561340.

11. Talukdar S, Kumar S, Bhatla N, Mathur S, Thulkar S, Kumar L. Neo-adjuvant chemotherapy in the treatment of advanced malignant germ cell tumors of ovary. Gynecol Oncol. 2014 Jan;132(1):28-32. DOI: 10.1016/j.ygyno.2013.10.009. Epub 2013 Oct 19. PMID: 24145115.

12. Park JY, Kim DY, Suh DS, Kim JH, Kim YM, Kim YT, Nam JH. Outcomes of pediatric and adolescent girls with malignant ovarian germ cell tumors. Gynecol Oncol. 2015 Jun;137(3):418-22. DOI: 10.1016/j.ygyno.2015.03.054. Epub 2015 Apr 1. PMID: 25842162.

13. Zanetta G, Bonazzi C, Cantù M, Binidagger S, Locatelli A, Bratina G, Mangioni C. Survival and reproductive function after treatment of malignant germ cell ovarian tumors. J Clin Oncol. 2001 Feb 15;19(4):1015-20. DOI: 10.1200/JCO.2001.19.4.1015. PMID: 11181664.

14. Vergote I, Amant F, Kristensen G, Ehlen T, Reed NS, Casado A. Primary surgery or neoadjuvant chemotherapy followed by interval debulking surgery in advanced ovarian cancer. Eur J Cancer. 2011 Sep;47 Suppl 3:S88-92. DOI: 10.1016/S0959-8049(11)70152-6. PMID: 21944035.

15. Berek JS, Renz M, Kehoe S, Kumar L, Friedlander M. Cancer of the ovary, fallopian tube, and peritoneum: 2021 update. Int J Gynaecol Obstet. 2021 Oct;155 Suppl 1(Suppl 1):61-85. DOI: 10.1002/ijgo.13878. PMID: 34669199; PMCID: PMC9298325.

16. Coleridge SL, Bryant A, Kehoe S, Morrison J. Neoadjuvant chemotherapy before surgery versus surgery followed by chemotherapy for initial treatment in advanced ovarian epithelial cancer. Cochrane Database of Systematic Reviews 2021, Issue 7. Art. No.: CD005343. DOI: 10.1002/14651858.CD005343.pub6.

17. Elies A, Rivière S, Pouget N, Becette V, Dubot C, Donnadieu A, et al. The role of neoadjuvant chemotherapy in ovarian cancer. Expert Rev Anticancer Ther. 2018 Jun;18(6):555-566. doi: 10.1080/14737140.2018.1458614. Epub 2018 Apr 10. PMID: 29633903.

18. Sato S, Itamochi H. Neoadjuvant chemotherapy in advanced ovarian cancer: latest results and place in therapy. Ther Adv Med Oncol 6 (6): 293–304 [Internet]. 2014. DOI: 10.1177/1758834014544891

19. Weinberg LE, Lurain JR, Singh DK, Schink JC. Survival and reproductive outcomes in women treated for malignant ovarian germ cell tumors. Gynecol Oncol 2011; 121:285–9

20. Li J, Wu X. Current Strategy for the Treatment of Ovarian Germ Cell Tumors: Role of Extensive Surgery. Curr Treat Options Oncol. 2016 Aug;17(8):44. DOI: 10.1007/s11864-016-0416-2. PMID: 27357180.

21. Zamani N, Rezaei PM, Ghasemian DS, Alizadeh S, Modares GM. Fertility sparing surgery in malignant ovarian Germ cell tumor (MOGCT): 15 years experiences. BMC Womens Health. 2021 Aug 4;21(1):282.

22. Johansen G, Dahm-Kähler P, Staf C, Flöter Rådestad A, Rodriguez-Wallberg KA. A Swedish Nationwide prospective study of oncological and reproductive outcome following fertility-sparing surgery for treatment of early stage epithelial ovarian cancer in young women. BMC cancer. 2020 Oct 19;20(1):1009. https://doi.org/10.1186/s12885-020-07511-y