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Review article

Challenges and opportunities to address the emerging burden of targeted therapies in ovarian cancer

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ABSTRACT

Ovarian cancer (OC) poses a significant socio-economic burden globally with the greatest impact observed in low-and-middle income countries (LMIC). Despite the survival benefit from targeted therapies such as bevacizumab and poly (ADP- ribose) polymerase (PARP) inhibitors, they are associated with high costs to patients and payers which widens the disparities between high and low-income countries. OC treatments may also cause significant morbidity from cytoreductive surgery through to the use of targeted therapies reducing quality of life (QoL). Innovative approaches are necessary to address the increasing burden from the cost and morbidity of OC treatment especially in LMIC. De-escalation of treatment without compromising oncological outcomes could be a strategy to reduce financial cost and morbidity. Moreover, de-escalation techniques integrating the knowledge of pharmacokinetics and pharmacodynamics for dose reduction should be incorporated into clinical trials to identify the minimum effective dose rather than the maximum tolerated with the goal of reducing clinical and financial toxicity. This review summarises the health and economic burden of ovarian cancer with particular reference to LMIC and proposes de-escalation of targeted therapy as a clinical and economic strategy in increasing accessibility and affordability with consideration of patient preferences.

1. Introduction

Amongst female reproductive tract cancers, ovarian cancer (OC) ranks third in incidence and is a leading cause of mortality (Sung et al., 2021). Countries with a high human development index (HDI) in Europe and the Americas account for the highest reported cancer related incidence and mortality while comparatively lower figures have been reported in countries with a low HDI such as those in Africa and Asia. Despite these differences, there is a disproportionately high fatality-to-case ratio in Africa and Asia which could be attributed to poorer health infrastructure for diagnosis and treatment (Sung et al., 2021; Renner et al., 2013). Patients in low-and-middle income countries (LMIC) face considerable barriers to accessing treatment for OC due to inadequate specialist surgical training in cytoreductive surgery (Algera et al., 2023), inadequate manufacturing infrastructure and a lack of reliable supply of anticancer drugs (Fundytus A et al., 2021).

In recent years, targeted therapies such as bevacizumab and poly (ADP- ribose) polymerase (PARP) inhibitors used in addition to cytoreductive surgery and chemotherapy have changed the OC treatment landscape with considerable improvement in survival rates (Lheureux et al., 2019). However, bevacizumab showed improvement in progression free survival (PFS) only while there was a clinically meaningful but not statistically significant overall survival (OS) with Olaparib in their respective clinical trials (Tewari et al., 2019; DiSilvestro et al., 2023). The side-effects of targeted therapies can also have a negative impact on quality of life (QoL) (Tewari et al., 2019; Ledermann et al., 2012) in addition to the high costs leading to increased financial burden on health services, insurance providers and patients (Mariotto et al., 2011). Although cytoreductive surgery and chemotherapy have been shown to be cost effective in OC treatment (Aletti et al., 2009; Tran et al., 2018) the evidence is less favourable for targeted therapies which are not cost effective in comparison to surgery and standard chemotherapy or routine surveillance at the current drug prices (Poonawalla et al., 2015).

As targeted therapies become the standard of care in the OC

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treatment pathway (Ledermann et al., 2024), the wider issues of access and affordability especially in countries with poor health infrastructure and LMICs should not be ignored. To address the problem, innovative and affordable strategies are necessary, however, the scale of the problem and its impact on health and society needs to be understood (Fig. 1). Health economic evaluations tailored to the financial and economic landscape of a population are also required. This article provides an overview of the health and economic impact of OC treatment and introduces the concept of treatment de-escalation as a clinical and economic strategy in addressing these issues.

2. Accessibility to treatment in ovarian cancer

In high income countries (HIC), infrastructure for diagnosis, treatment and follow up for OC are more readily available and patients are more likely to receive care according to guidelines although disparities still persist (Algera et al., 2023; Karanth et al., 2019). OC patients in LMICs however, face greater barriers to accessing evidence-based OC care (Algera et al., 2023). There are relatively limited primary data from LMICs on this subject but available data suggest that the reasons are multifaceted (Reid et al., 2024). Some of the cited reasons include presentation with advanced disease, unavailability of infrastructure for diagnosis, poor access to specialist diagnostic expertise such as histopathology and radiology, lack of specialist surgical and medical oncology expertise, inconsistent supply of chemotherapeutic agents and limited supply or unavailability of targeted therapies (Algera et al., 2023; Fundytus A et al., 2021). Furthermore, even anticancer drugs identified as priority medicines on the World Health Organisation's (WHO) essential medicines list may not be readily available in LMICs (Fundytus A et al., 2021). Drug approvals in LMICs can also take a considerable amount of time, often many years after FDA approvals in the USA (Miller et al., 2021). It has also been suggested that some of these drugs may not be prioritised by LMICs due to the marginal survival benefits gained from them. Even when drugs are approved in these countries, the high cost of drugs like targeted therapies remain a major deterrent to access (Fundytus A et al., 2021). The introduction of biosimilars and generic anticancer drugs is one approach adopted by some countries to address this problem. The use of biosimilars in both HIC and LMIC for instance has generated significant cost savings which has led to increased availability and access to targeted therapies. Nonetheless, treatment remains unaffordable to most of the population in LMICs due to lack of insurance cover and the high out of pocket (OOP) payments associated with accessing care (Dhankhar et al., 2021).

3. Cost of ovarian cancer treatment and financial toxicity

OC care is evolving into the management of a chronic illness with additional treatment offered at each recurrence to prolong PFS and OS (Lheureux et al., 2019; Bodurka-Bevers et al., 2000). Most of the data on the cost of OC care to insurance providers and OOP cost to patients come from the USA. Bercow *et al.*, (2019) estimated a median total medical expenditure of $93,632 during the first year following index surgery, of which approximately 3 % ($2988) was borne OOP by patients (Bercow et al., 2017). Expenditure was highest in the first 6-months, coinciding with the need and high cost of inpatient postoperative care during the first 30 days through to completion of chemotherapy (Bercow et al., 2017). A study by Calhoun *et al.*, (2001) evaluated the cost associated with neurotoxicity, nephrotoxicity and thrombocytopenia secondary to chemotherapy for OC. They found that the indirect cost to patients and caregivers from loss of employment and productivity contributed substantially to the financial burden (Calhoun et al., 2001).

Studies have also shown that the use of targeted therapies such as bevacizumab and PARP inhibitors are associated with a significant increase in the treatment expenditure for OC. In comparison to chemotherapy regimens without bevacizumab (a drug shown to increase PFS but not OS (6)), the addition of bevacizumab was associated with an increase in mean total medical expenditure of $66,986 in the first 8-months of treatment ($p < 0.001$). It also increased OOP costs by $229 ($p < 0.001$) over the same period (Suidan et al., 2019). Between the year 2014–2017, the total cost per month for PARP inhibitors to the insurer

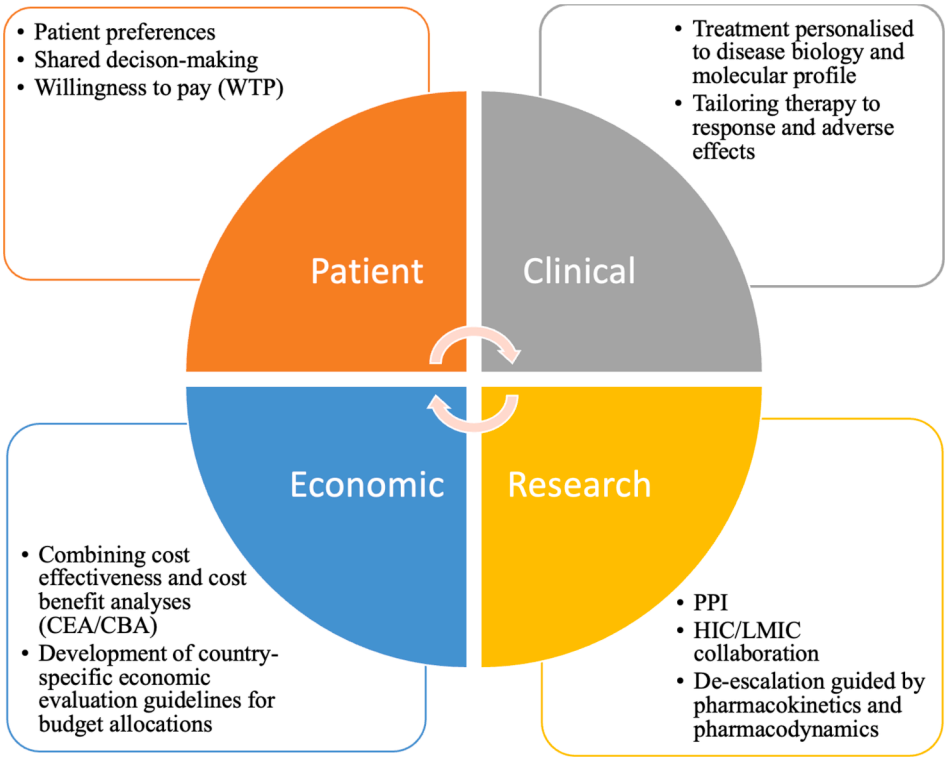

Fig. 1. Strategies to address the burden of targeted therapies.

was approximately $13,000, while OOP cost to patients varied from no cost to more than $2000 per month (Liang et al., 2021; Harrison et al., 2021). PARP inhibitors were also the costliest health expenditure in OC management when compared to other expenses such as laboratory investigations and imaging and accounted for up to 8.7 % of patients' monthly household income expenditure (Harrison et al., 2021). Although these figures suggest that the insurer bears most of the cost of treatment, it is important to note that over the course of the disease from diagnosis to multiple relapses, the OOP costs accumulate and sum to a substantial amount (Harrison et al., 2021).

3.1. Financial toxicity

'Financial toxicity' in oncology, as a consequence of OOP expenditure from cancer diagnosis and related treatments, has negative psychosocial and survival outcomes in those affected (Carrera et al., 2018). The prevalence of financial toxicity in LMIC ranges from 18 to 93 % and risk factors include household size ≥ 4, attending a private health clinic, multiple cycles of chemotherapy and long length of hospital stay (Donkor et al., 2022). In the USA, financial toxicity in gynaecological cancers was associated with younger age, advanced disease, Black/Hispanic race, chemotherapy, low income, non-private health insurance, multiple outpatient visits and longer hospital stay ≥ 20 days (Aviki et al., 2022; Bouberhan et al., 2019). In Malaysia, an upper middle-income country, gynaecological cancers were associated with significant OOP and catastrophic health expenditure (CHE) exceeding 10 % of the annual household income leading to impoverishment of households after commencing treatment (Liew et al., 2022). Although individual cost and impact of OC were not reported separately in the study conducted in Malaysia, the results bear similarities to the study by Liang *et al.*, (2021) conducted in the USA where 40 % of OC patients were in the 'catastrophic phase' of co-sharing payments with the insurer by the second PARP inhibitor prescription i.e., second month of treatment (Liang et al., 2021) highlighting the increasing financial burden over time.

Notably, patients in public healthcare funded systems also experience financial hardship. In a Dutch study, up to 16 % of gynaecological cancer survivors experienced financial toxicity (Pearce et al., 2019) while a systematic review of cancer diagnosis in publicly funded healthcare countries including Australia, UK, Netherlands and South Korea reported loss of income in the range of 18–67 % with OOP costs between US$17- $506 per month and financial toxicity in the range of 22–27 % (Longo et al., 2020). This systematic review did not include OC patients; however, it demonstrates the impact of cancer diagnosis and associated financial hardship even in countries with a public funded healthcare structure.

4. Quality of life with OC treatment

4.1. Surgery

Although studies on QoL after ovarian cancer surgery are sparse (Kumar et al., 2019) primary cytoreductive surgery for OC is known to be associated with great perioperative morbidity especially in cases of high disease burden and surgical complexity (Xu et al., 2020) due to multi-organ resection including bowel, liver, spleen and diaphragm which may be required. Available retrospective and prospective observational studies have reported that postoperative morbidity associated with cytoreductive surgery decreases as patients recover and surgery is associated with increased PFS thereby justifying maximal surgical effort (Xu et al., 2020; Sundar et al., 2022).

For instance, the SOCQER-2 multicentre study investigating patient reported health related QoL (HRQoL) using validated questionnaires (EORTC QLQ-C30 (Aaronson et al., 1993) and EORTC QLQ-OV28 (Greimel et al., 2003) across patients with low, intermediate and high surgical complexity scores (SCS) demonstrated that HRQoL was significantly reduced in the first 6-months after surgery with high SCS. However, patient reported outcomes were similar across all groups by 12-months (Sundar et al., 2022). Similarly, a systematic review and *meta*-analysis comparing upfront cytoreductive surgery with interval cytoreductive surgery showed no difference in HRQoL but most importantly, QoL scores were similar and maintained at 6–9 months after treatment in both groups (Kumar et al., 2019).

4.2. Systemic treatment

Chemotherapy plays a significant role in improving prognosis in both primary and relapsed OC, but a National Cancer Database study in the USA reported that up to 2 % of OC patients refuse treatment (Sundar et al., 2022). Whilst there are likely to be many reasons for this, there is evidence on the impact of chemotherapy on HRQoL during the treatment phase which could influence patients' decision making. Pergialiotis *et al.*, (2022) conducted a systematic review evaluating patient reported HRQoL using the EORTC QLQ-C30 at various stages of chemotherapy from baseline to follow up after completion of treatment. Several studies included in this systematic review reported an increase in global health status, social and emotional wellbeing and a reduction in pain over the course of chemotherapy. Fatigue, insomnia, nausea and vomiting were persistent; although with some improvement with progression of therapy in fatigue and insomnia, while nausea and vomiting improved only after completion of chemotherapy (Pergialiotis et al., 2022). These data are reassuring as they demonstrate that most patients are able to tolerate chemotherapy with improvement in symptoms and a reduction in associated side-effects over the course of treatment.

PARP inhibitors are also associated with side-effects, which depending on severity, have led to treatment interruption or discontinuation in the range of 15–55 % (Ledermann et al., 2012; Mirza et al., 2016; Coleman et al., 2017). Primary studies on patient reported outcomes (PROs) and HRQoL with PARP inhibitors are lacking but they have been included in PARP inhibitor trials as exploratory secondary endpoints. Given the clinical benefit derived from PARP inhibitors in prolonging PFS and OS, one might expect significant improvements in HRQoL over placebo. Piepert *et al.*, (2023) reported the NFOSI-18 Disease Related Symptoms – Physical (DRS-P) (Jensen et al., 2011), total score, and side-effect bother in the ARIEL3 cohort (Peipert et al., 2023). They found that in comparison with placebo, rucaparib was associated with greater deterioration from baseline with patients experiencing moderate to high side-effects up to 20 % of the time over the course of the study (Peipert et al., 2023). Similarly, a review summarising the HRQoL analysis in PARP inhibitor trials showed a trend towards improvement in time without symptoms or toxicity (TWiST) with PARP inhibitors but there was no statistical or clinically significant difference in overall HRQoL and disease related symptoms over placebo. For instance in the SOLO 2 trial, (olaparib maintenance vs placebo in platinum sensitive relapse OC) which used the EQ-5D-5L (Herdman et al., 2011) and Functional Assessment of Cancer Therapy-Ovarian (FACTO) (Basen-Engquist et al., 2001) questionnaires, the mean change from baseline over the first 12-months was -2.90 (95 % CI − 4.13 to − 1.6) with Olaparib while placebo was −2.87 (− 4.64 to − 1.10) (estimated difference − 0.03; 95 % CI − 2.19 to 2.13; p = 0.98) (Fiteni and Peron, 2022). It is important to note that these trials were not designed specifically to measure HRQoL with PARP inhibitors, therefore, could be underpowered to detect a difference and each trial used different tools to measure HRQoL limiting the scope to pool results across studies.

5. Treatment de-escalation to improve QoL and reduce costs

5.1. Dose de-escalation

Clinical benefits derived from chemotherapeutic agents and targeted therapy may be offset by both financial toxicity and the adverse effects of treatment on patients. Researchers have been exploring ways to de-

escalate treatment with the aim of identifying 'overtreatment' and curtailing its use. The focus is also shifting towards identifying the minimum effective dose, thereby reducing financial toxicity and improving HRQoL through the reduction in treatment adverse events without loss of long-term survival benefits (Piccart et al., 2020). A number of these studies have been conducted by shortening the duration or omission of chemotherapy in breast, oropharyngeal and colorectal cancers with variable success (Earl et al., 2019; Pivot et al., 2013; Cardoso et al., 2016; André et al., 2013). De-escalation of therapy is also an active area of research in OC with trials evaluating de-escalation techniques such as the introduction of PARP inhibitors in the neoadjuvant setting instead of chemotherapy and the use PARP inhibitors in the adjuvant setting with reduction in cycles of chemotherapy (Caruso et al., 2023).

Treatment de-escalation can also be achieved by the reduction of the drug dosing schedule guided by its pharmacodynamic and pharmacokinetic activity. In a pre-clinical model, Murray *et al.*, (2014) demonstrated rapid accumulation and retention of rucaparib in tumour cells for 3 days after the last dose was administered. They also showed that a single dose equivalent to 5 daily doses per week maintained therapeutic PARP inhibition in tumour xenografts (Murray et al., 2014) Smith *et al.*, (2022) investigated this further by comparing the activity of rucaparib with 4 other PARP inhibitors-olaparib, niraparib, talazoparib and pamiparib in human OC cell lines. Rucaparib maintained persistent PARP inhibition beyond 72 h in the drug-free medium in both IGROV-1 and ES-2 cell lines while the activity of the other PARP inhibitors was significantly lower (Smith et al., 2022). These findings are encouraging and support the concept of an alternative dosing schedule and the potential for de-escalation of rucaparib with anticipated reduction in adverse events and costs. Preliminary results of a real-world feasibility study (IPIROC) investigating intermittent dosing of rucaparib (twice a week) in recurrent platinum sensitive OC showed promising results with reduction in haematological toxicity and patient preference for the reduced regimen due to affordability in the LMIC setting (Mukhopadhyay et al., 2023). The NORA trial conducted in China demonstrated the efficacy and safety of individualised starting dose of niraparib of 200 mg/day or standard 300 mg/day dependent on baseline body weight and platelet count (Wu et al., 2021). Similarly, a retrospective study on niraparib dose reduction which included both 200 mg/day and 100 mg/day dose reductions also showed no detriment in PFS and safety of the reduced dose in both patients with primary and recurrent OC (Bruno et al., 2024). These findings are encouraging but well-designed clinical trials are still required to confirm the hypothesis of a reduced drug administration schedule of PARP inhibitors and other targeted agents for OC.

The use of PARP inhibitor maintenance therapy in homologous recombinant deficiency (HRD) negative and BRCA- wild type OC patients in comparison with no treatment is also an aspect of treatment de-escalation that could be explored. Current guidelines recommend maintenance therapy with niraparib or rucaparib in platinum sensitive OC irrespective of HRD and BRCA status (Ledermann et al., 2024). This approach potentially reduces the need for biomarker testing especially in low resources settings where testing facilities may not readily be available (Sharma et al., 2023). However, a gain in 3 months PFS in the HRD negative patients (González-Martín et al., 2019) versus the associated financial and clinical toxicity cannot be justified in low resource settings. Therefore, limiting treatment to biomarker positive patients could be a de-escalation strategy in LMICs but thorough counselling and shared decision making with biomarker negative patients is necessary in making an informed choice for maintenance treatment.

5.2. Patient perspective

The concept of treatment de-escalation to reduce clinical toxicity without compromising on efficacy is based on biological plausibility but must be conducted cautiously due to the lethal nature of OC. Although clinicians and researchers recognise the importance of treatment de-escalation in OC, studies evaluating the patients' preferences on the subject are lacking. In shared decision-making between the clinician and patient, it is necessary that adequate information is provided to patients regarding their diagnosis, management options and anticipated outcomes while taking into consideration their preferences and values on the proposed plan of care (Williams et al., 2020). The decision-making process should be tailored to each individual's preferences as the effects of different treatment modalities may influence patients' decision to commence and remain on treatment. Maintaining employment, productivity, and mental and emotional wellbeing, whilst minimising loss of independence, need for carers and financial impact of treatment are all factors affecting QoL and all may influence patient decision-making (Williams et al., 2020; CancerCare. Patient Access Engagement Report. New York;, 2016).

With a cancer diagnosis, patients are often faced with making a choice between treatment options which could have a significant impact on both QoL and length of life. For instance, choosing palliative chemotherapy with known toxicity to prolong survival over watchful waiting (Koedoot et al., 2003) or making trade-offs between frequency of treatment, mode of administration, side-effects and cost (Beusterien et al., 2014; Williams et al., 2021).

Studies on patient preferences in breast cancer have shown that patient perception about treatment de-escalation can be complex and thorough counselling is important in aiding their understanding of this concept. For instance, Rocque *et al.*, (2021) found that without adequate counselling, patients may perceive treatment de-escalation negatively. They may view treatment de-escalation trials with fear of recurrence and regret and anxiety due to deviation from the standard of care (Rocque et al., 2021). The choice of words may be problematic as de-escalation could be perceived by patients as choosing a less efficacious option or in some cases, giving up on treatment all together (Rocque et al., 2021; Andrews et al., 2022). The use of patient-centred words such as 'personalised', 'optimised', 'minimum effective dose' or 'reduced chemotherapy' is preferred. Reduction in side-effects and risk of long-term disability, improvement in QoL, less OOP costs and trust in the clinician were reported as the main facilitators for patient engagement with treatment de-escalation (Rocque et al., 2021). Similarly, preferences may differ depending on the stage of treatment as demonstrated by a patient and public involvement (PPI) study for a willingness to pay (WTP) survey in OC which showed that patients have different expectations of treatment in primary versus recurrent disease (Abdul-Aziz et al., 2024).

5.3. Economic perspective

As innovative treatment technologies are introduced to the clinical setting, the financial burden on health insurance providers and OOP costs to patients are likely to increase globally (Mariotto et al., 2011). De-escalation of treatment has the potential to alleviate the financial and economic burden of OC especially in the LMIC setting where cost of care is a significant barrier. However, clinical and economic decisions on de-escalation should be guided by robust clinical trials and economic evaluations on the trade-offs between cost and benefits of a new intervention or regimen such as de-escalation versus the current standard of care. Whilst cost effectiveness analysis (CEA) and its variant, cost utility analysis (CUA) are more commonly used in health economic evaluations in OC (Zhong et al., 2018; Nie et al., 2023; Gonzalez et al., 2020), the cost benefit analysis (CBA) approach could be a more suitable tool, either used alone or in combination with a CEA especially in LMICs and low resource settings. The measure of benefit of an intervention (value to respondents) in a CBA is often estimated by the respondents' WTP (Drummond et al., 2015; Hanley et al., 2003). WTP can also be used independently outside the context of a CBA to estimate the market price of an intervention and in the prediction of future demand (O'Brien and Gafni, 1996). It is therefore important that future studies are designed to

understand patients' preferences for competing methods of treatment with their impact on QoL, survival and cost which could be incorporated in subsequent health economic evaluations.

6. Conclusions

OC poses a significant burden from both health and economic perspectives and the problem is amplified by inequalities in access and affordability of treatment. Targeted therapy for OC is costly and is associated with a significant financial burden on both patients and healthcare funders. Treatment de-escalation appears to be a promising area of research in OC and clinical trials should be designed to evaluate the safety and effectiveness of treatment de-escalation. Multiagency stakeholder involvement of researchers, clinicians, funders and patients is necessary to support the translation of research hypothesis into clinical practice.

CRediT authorship contribution statement

Salamatu Abdul-Aziz: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation. **Nawaraj Bhattarai:** Writing – review & editing, Supervision. **Luke Vale:** Writing – review & editing, Supervision. **Gurdeep S Sagoo:** Writing – review & editing, Supervision. **Asima Mukhopadhyay:** Writing – review & editing, Visualization, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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