



**THE SOCIETY OF GYNECOLOGIC ONCOLOGY OF CANADA (GOC)
POSITION STATEMENT AUGUST 2017
THE USE OF PARP INHIBITORS IN THE TREATMENT OF
RECURRENT HIGH-GRADE OVARIAN CANCER**

**Note: The term “ovarian” cancer, as used in this paper, refers to a family of cancers that originate in the ovary, the fallopian tube and/or the peritoneum.*

OUR POSITION

- PARP inhibitors represent a major advance as they provide meaningful outcome benefits and have easily manageable, low grade toxicity.
- PARP inhibitors should be made available to Canadian women for the treatment of recurrent high grade ovarian cancer consistent with Health Canada approvals.

SUMMARY STATEMENT

Despite high rates of response to chemotherapy and surgery, most patients with ovarian cancer ultimately recur, undergo further treatments and ultimately succumb to the disease. A new class of drugs, called PARP inhibitors, represents a significant step forward in the treatment of ovarian cancer. Health Canada has approved one PARP inhibitor for patients carrying a mutation in the BRCA 1 or 2 genes, and several other PARP inhibitors have shown equally good results and are undergoing evaluation by the health authorities.

What makes PARP inhibitors unique is their ability to exploit DNA repair deficiencies in ovarian cancer cells. In contrast to many chemotherapeutic agents, PARP inhibitors have low rates of side effect and these are easily manageable.

As with most novel molecular therapies, PARP inhibitors are costly. The gynecologic oncology community recognizes the need to use PARP inhibitors judiciously, targeting those patients who stand to benefit from them. If funding will not be provided, eligible patients will be deprived of the opportunity to benefit from them, because PARP inhibitors, in the right patients, delay the regrowth of their cancers and maintain the quality of life of being without evidence of disease.

This statement reflects GOC’s position, based upon currently available evidence.

- Recently completed PARP inhibitor studies confirm the large degree of benefit in delaying the time to when the cancer next starts to re-grow in ovarian cancer patients whose cancers have returned, especially but not exclusively in those with BRCA mutations.

- To be in accord with the Canadian health care system's high standards of care, PARP inhibitors should be incorporated into the treatment options for ovarian cancer.
- PARP inhibitors are best used as continuation therapy (also called maintenance treatment) after successful re-use of chemotherapy for ovarian cancer that had regrown following initial chemotherapy in selected patients (patients with BRCA mutations and platinum sensitive disease as per the recommendations of Health Canada). This strategy provides the greatest absolute benefit in maintaining a high quality of life and in delaying cancer progression.
- PARP inhibitors may also have value when used on their own as an alternative to standard chemotherapy. However, this is not a currently approved indication.

BACKGROUND AND SUPPORTING DATA

Deficient DNA repair mechanism is present in about 50% of high-grade ovarian cancers. Mutations in BRCA genes, either acquired or inherited, account for about 40% of these repair-deficient cancers, with the remaining 60% arising from other abnormal genes.

PARP inhibitors work by blocking a protein called PARP, which under normal conditions helps to maintain DNA integrity¹. When a deficiency in DNA repair exists in the ovarian cancer cells, PARP inhibition leads to the cell death of the cancer cells, while sparing normal cells that do not have a deficiency in DNA repair¹.

Evidence for approved indication

Health Canada approved the PARP inhibitors as continuation therapy based on the results of a randomized placebo-controlled phase 2 study in patients with recurrent platinum-sensitive high-grade ovarian cancer (Study 19)^{2,4}. Since the approval, two subsequent phase 3 studies, confirmed the effectiveness of PARP inhibitors (ENGOT trial³ and SOLO2⁹).

In subjects with inherited BRCA mutations, median progression-free survival improved from 4 to 11 months (HR = 0.18) in Study 19¹, from 6 to 21 months in ENGOT (HR = 0.27)³, and from 5.5 to 19 months in SOLO 2 (HR=0.30). In view of the different inclusion criteria in these studies, PARP inhibitors can at present be considered comparably effective.

Subgroup analyses suggest that ovarian cancer patients without BRCA mutations may also benefit from treatment: progression-free survival in BRCA-non-mutated patients improved from 5 to 7 months in Study 19¹ and from 4 to 9 months in ENGOT³. Further analyses in ENGOT revealed that these improvements occurred in BRCA-non-mutated individuals with and without evidence of abnormal DNA repair.

At present, there are insufficient long-term data to allow for a fully reliable statistical analysis of overall and longer-term survival benefits from PARP inhibitors, although preliminary results are encouraging.

Lack of toxicity is especially important for agents used as maintenance therapy, and studies have found that PARP inhibitors are well tolerated. Common side effects include low grade nausea, fatigue, vomiting, diarrhea, distorted taste, indigestion, headache, and decreased appetite. These effects are often transient and can easily be managed with a dose reduction. The possibility of a slight increase in the risk of myelodysplasia/acute myeloid leukemia, which can be fatal, has been raised.

Other uses

PARP inhibitors also have activity when used alone in later on in the sequence of treatments, in a manner akin to standard chemotherapy^{5,6,7,8}. In Study 45, the highest response rates occurred in subjects with BRCA mutations (40%), with those patients who responded to platinum-based chemotherapy benefitting the most. Of note, about 10% of patients had a much more durable length of response to PARP inhibitors than is the expected norm achievable with standard chemotherapy. In a small study of BRCA-positive ovarian cancer, subjects had similar responses to PARP inhibitors vs chemotherapy with liposomal doxorubicin⁶.

PARP inhibitor monotherapy offers the highest benefit in patients with BRCA mutations, but also offer benefits to some people without BRCA mutations but who responded to platinum based chemotherapy, suggesting that platinum sensitivity may serve as a surrogate marker for predicting benefit.

To date, efforts to combine cytotoxic chemotherapy with a PARP inhibitor have proven challenging due to substantial toxicity.

Ongoing and future research will elucidate with greater accuracy the degree of benefit from PARP inhibitors as stand-alone therapy and may uncover additional roles for these agents (for example, as maintenance treatment after first-line surgery/chemotherapy). Such research will enable the drug class to be used both effectively and responsibly.

CONCLUSION

The Society of Gynecologic Oncology of Canada (GOC) recommends that PARP inhibitors be made available to Canadian women for the treatment of recurrent high grade ovarian cancer consistent with Health Canada approvals. The PARP inhibitors represent a major advance as they provide meaningful outcome benefits and have easily manageable, low grade toxicity. GOC, in addition, advocates for ongoing assessment of their role as new evidence becomes available in order to ensure Canadian women with ovarian cancer with the very best treatment.

On behalf of The Society of Gynecologic Oncology of Canada,



Walter H. Gotlieb, MD, PhD
President



Paul J. Hoskins, MA, FRCPC
Past-President

References

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OUR MISSION

The Society of Gynecologic Oncology of Canada is a non-profit organization consisting of physicians, nurses, scientists and other health care professionals specializing in gynecologic oncology. Its purpose is to improve the care of women with or at risk of gynecologic cancer by raising standards of practice, encouraging ongoing research, promoting innovation in prevention, care and discovery, and advancing awareness. GOC also seeks to disseminate knowledge to practitioners, patients and the general public on gynecologic cancer as well as cooperate with other organizations committed to women's health care, oncology, and related fields.