THE SOCIETY OF GYNECOLOGIC ONCOLOGY OF CANADA | LA SOCIÉTÉ DE GYNÉCO-ONCOLOGIE DU CANADA

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GOC POSITION STATEMENT REGARDING
THE USE OF PARP-INHIBITORS IN THE TREATMENT OF RECURRENT HIGH GRADE SEROUS OVARIAN CANCER

Summary

The use of PARP inhibitors was discussed at our December 2014 GOC meeting. The universal consensus was that PARP inhibitors would be a useful treatment option for BRCA positive women with platinum sensitive, relapsed epithelial ovarian cancer. This family of drugs is a treatment advance and importantly, a small subset of patients treated with a PARP inhibitor had unexpectedly long durations of remission/benefit which we would not expect to see with standard chemotherapy. Since this meeting, both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have approved olaparib. The FDA approved it as a stand-alone therapy and the EMA approved it as maintenance therapy for women with platinum sensitive recurrent ovarian cancer who have a mutated BRCA gene, and who have responded to their latest round of chemotherapy. It is not clear as yet to the members of GOC as how to most effectively use PARP inhibitors. There are multiple, soon to be completed studies which will provide more information. Important as yet unanswered questions are: 1) are there patients without inherited BRCA mutation that could also benefit and 2) would the drugs be more effectively used as an alternative to standard chemotherapy instead of as maintenance therapy after completing standard chemotherapy.

Supporting Data

PARP inhibitors work by blocking the ability of cells to repair single-stranded DNA breaks. Unrepaired, these single-stranded breaks are converted to double-stranded breaks. In women with BRCA mutated, high grade serous epithelial ovarian cancer (EOC), homologous recombination (HR), which repairs these double stranded DNA breaks, is absent. These double-stranded breaks, resulting from the PARP inhibition, cannot then be repaired and the tumor cell dies (Synthetic Lethality). It is estimated that between 10-15% of women with EOC have mutations in the BRCA genes. Other DNA repair mechanisms may be affected in up to another 50% - so called BRCAness.

To date, trying to combine cytotoxic chemotherapy with a PARP inhibitor at the same time has proven challenging due to substantial toxicity issues PARP inhibitors either as single agents alone or as maintenance therapy post standard chemotherapy seem the most beneficial strategies.

Approval was granted by the FDA and EMA following review of data from a single, randomized, phase II study of maintenance (olaparib versus placebo in patients with platinum-sensitive EOC {Study 19}). Olaparib is one of the PARP inhibitors in development. There was an improvement in progression free survival (PFS) from 4.8 to 8.4 months (HR=0.35). Analysis of overall survival (OS) did not show a benefit. Subgroup analysis showed a clinically meaningful increase in PFS of 6.9 months, in those women with a known BRCA mutation (somatic or germline). Again, analysis of OS demonstrated no statistically significant improvement but there was a 3 month increase in the median from 31.9 to 34.9 months. As yet there is insufficient long term data to allow for a fully reliable statistical

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comparison and its analysis is further confounded by cross-over as 23% of patients in the placebo group went on subsequently to receive a PARP inhibitor.) Study19 together with other studies have shown that PARP inhibitors, as a class, are well tolerated. Common side effects include low grade nausea, fatigue, vomiting, diarrhea, distorted taste, indigestion, headache, and decreased appetite. These side effects often improve over the first month and are easy to control by dose reduction. Non-toxicity of treatment is essential when it is to be used in the maintenance setting as these women would otherwise be well with a high quality of life score.

PARP inhibitors also have activity as single-agents. Response rates were highest in those with BRCA mutations – 40%. Response in the BRCA mutated was seen in both the platin sensitive and resistant subsets – 50% versus 30%. PARP inhibitors may also be of benefit in a broader population than this. BRCA mutations can occur in the tumor alone (i.e. due to a somatic mutation as opposed to the inherited or germ line mutation) and there can be loss of HR from other mechanisms, i.e. BRCAness. In study 19, 14% of women had a somatic mutation alone and the efficacy data was similar to that in the women with germline mutations. With regard to BRCAness, the response rate in those without mutations was 24% in the Gelmon trial. However if the individual was BRCA negative and also had platinum resistant disease then response was rare, less than 5%, ie: platin sensitivity may serve as a surrogate for BRCAness.

One small randomised phase II study compared olaparib to liposomal doxorubicin. Both the progression free and overall survivals were similar with the PARP inhibitor and the liposomal doxorubicin.

Currently multiple phase III studies are examining the role of PARP inhibitors in women with EOC. These address the benefits of maintenance therapy following either first-line or second-line therapy in women with either platinum-sensitive or platin resistant disease. Studies trying to identify simple tests that define BRCAness and whether PARP inhibitors work in this subset of patients are also ongoing.

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