Multicentre Italian Trials in Ovarian cancer
MITO

Meeting in FAD sincrona
18-23-25 Febbraio 2021

XXXVI^ RIUNIONE NAZIONALE MITO

Phase II study of oral Melphalan in two cohorts of BRCA-related or BRCA wt platinum-resistant epithelial ovarian carcinoma (EOC)

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Background

- Melphalan is a nitrogen mustard-like alkylating agent mainly used in the therapy of multiple myeloma. Very little information is available to chemotherapy with melphalan as treatment of EOC.
- Melphalan, considered as a bifunctional alkylating agent that induces inter- and intrastrand DNA cross-links (Fig.1), has been shown to be selectively efficient in only BRCA-deficient cases reports of EOC to date.

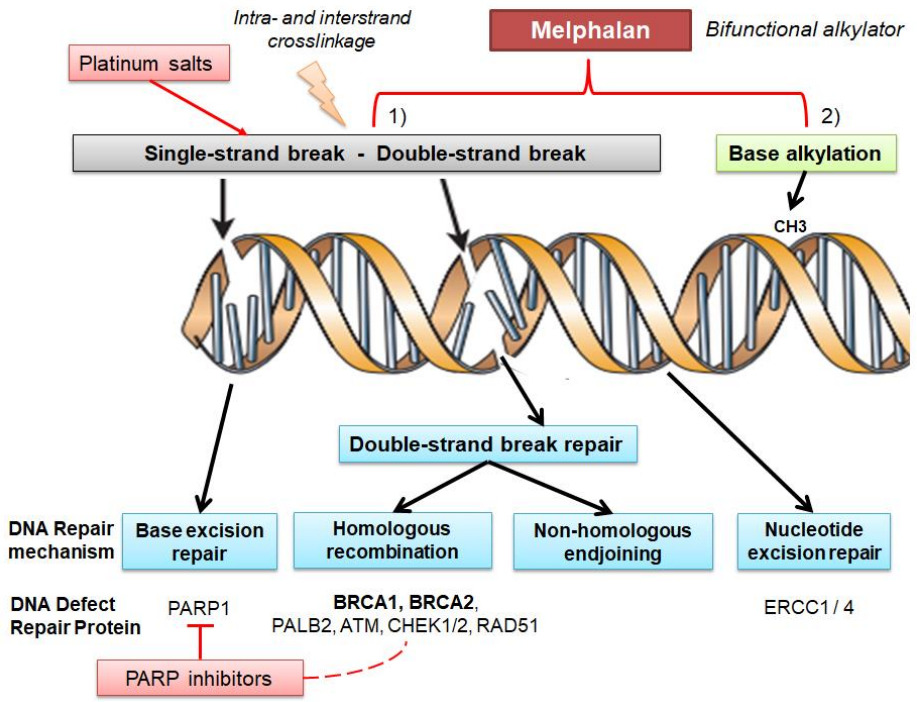

Fig 1. Melphalan and DNA repair mechanisms

- **Preliminary data:**

✓ We performed a retrospective single-center case series (submitted) of 75 patients with platinum-resistant EOC receiving melphalan at IRST (Feb 2007-Jul 2020). Median PFS and OS of 3.5 months (range 1-44) and 8.4 months (range 1.1-63), respectively. We had BRCA status (somatic and/or germline) from 36 patients showing 11 (28%) BRCA mutant patients.

✓ In the EOC patients harboring molecular data, we observed a significantly longer PFS and OS (HR=3.16, 95% CI 1.58-6.33, p=0.0013, and HR=2.39, 95% CI 1.58-5.42, p=0.028, respectively) in BRCA1/2 mutant compared to BRCA1/2 deficient melphalan-treated patients.

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Phase 2 study proposal

- This is a prospective, multicenter, non-randomized single-arm trial.
- Patients with recurrent somatic or germline BRCA-mutated ovarian cancer and/or BRCAwt phenotype will be prospectively enrolled and treated with melphalan every 4 weeks.
- Patients will be stratified according to the BRCA-mutational status.
- Other inclusion criteria will be: age ≥18 years, Eastern Cooperative Oncology Group (ECOG) PS≤2, measurable disease, life expectancy >3 months, absolute neutrophil count (ANC) >1500/mm3; platelets count >100 000/mm3 ; bilirubin and creatinine levels 5 days) G4 neutropenia and febrile G3 neutropenia and in the case of ≥ grade 3 non haematologic toxicity.
- The primary end point of the trial will be the clinical benefit defined as PR/CR and stable disease (SD) lasting at least 18 weeks.
- All patients receiving at least one melphalan dose will be considered assessable toxicity. Treatment-related toxicity will be assessed according to NCI-CTC criteria version 4.3.
- Treatment response will be evaluated according to RECIST version 1.1 criteria every three cycles.

Study design

- Two cohorts of platinum-resistant ovarian cancer BRCA mutated and BRCAwt patients.
- In an explorative intent possible to consider to study HRD panel when possible in most of cases.
- Sample size to be determined based on the number of enrolled Centers.

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