Bcl-2 proteins expression and response to navitoclax in platinum resistant/refractory recurrent ovarian cancer (PROC)


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Background: Here is no convincing active treatment for patients with PROC. Anti-apoptotic bcl-2 proteins have been implicated in chemotherapy (CT) resistance. In pre-clinical studies, we demonstrated promising activity of Navitoclax, an anti-apoptotic inhibitor of Bcl-2 family, in ROC tumors, suggesting a potential action in platinum resistant pts. We conducted a multicentric phase II trial of Navitoclax monotherapy and reported modest efficacy (ESMO 2017, abstract #2269). Here we aimed to describe the relationship between Bcl-2 protein expression and response to Navitoclax; we also reported response to subsequent line of CT.

Methods: Pts (N = 46) with high grade serous PROC received oral Navitoclax (150 mg daily for 7 days followed by 250 mg daily) until disease progression or toxicity. All pts had a biopsy of relapsed disease before navitoclax initiation to assess the expression level of Bcl-2 proteins by histomunnochemistry (IHC), as low, medium or high. We first evaluated the efficacy of Navitoclax for pts with high BIM level, then with high BIM expression combined with low Mcl-1 and/or phospho-ERK. Response to subsequent CT was also described.

Results: 44 pts (with median of 4 prior lines) were assessable for efficacy: PFS was 50 days [6-234] with 1 partial response (PR), 15 stable diseases (SD). IHC data were available for 35 pts. BIM was highly expressed in 9 pts, 4 of them with PR/SD (p = 0.68). Among them, 7 had a low expression of Mcl-1 and/or phospho-ERK, of whom 4 with PR/SD, showing no evidence of relation with clinical response. After Navitoclax, 32 pts were retreated with CT: 4PR and 9SD were noted, including 11 pts with long response (6-13 months.). Median delay from previous platinum-based treatment to subsequent CT was 9 months [2-23] for PR/SD pts. Especially, 12 pts received platinum after Navitoclax with high response rate (3PR/4SD, 50%); median delay from previous platinum-CT was 18 months.

Conclusions: BIM expression, alone or combined with Mcl-1 and/or pERK, is not predictive of Navitoclax benefit. High proportion of PROC pts response to platinum rechallenge; the potential implication of Navitoclax needs further explorations. Other Bcl-2 family proteins (activator BH3-only BID and PUMA) expression may be more relevant. This trial is granted by the French Cancer Research Hospital Program in 2011 and the Maitzapia Bressan award in GINEGEPS 2014.


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