Current Trends in Biomedical Engineering & Biosciences

Juniper Publishers key to the Researchers

Review Article
Volume 1 Issue 2 - December 2016

Curr Trends Biomedical Eng & Biosci

Advances in the Therapy of Advanced Ovarian Cancer-Special Emphasis on the PD1/PDL1 Pathway

Kulvinder Kochar Kaur[1]*, Gautam Allahbadia[1] and Mandeep Singh[2]

[1]*Scientific Director, Centre for Human Reproduction, India*

[2]*Consultant Neurologist, Centre for Human Reproduction, India*

Submission: December 09, 2016; **Published:** December 20, 2016

***Corresponding author:** Kulvinder Kochar Kaur, Scientific Director, Centre for Human Reproduction, India, Tel: 91-181-9501358180; Fax: 91-181-4613422; Email: kulvinder.dr@gmail.com

Abstract

Ovarian Cancer gets diagnosed in advanced stage in 75% of patient and thus remains one of the most lethal gynecological malignancies. Despite 80% patients being responsive to platinum based chemotherapies to start with most relapse finally. Hence need of the hour is to find more effective immunotherapy's to be added to these CRT. Programmed cell death1 (PD1) -PDL1 is an important immune pathway which is discussed in detail along with role of nivelumab (a monoclonal antibody against PD1) and addition of other immunotherapy's like bevacizumab, Olafarib (A PARP (polyadenosine diphosphate (ADP)-ribose- inhibitor), C edinarib (a VEGF123 inhibitor) etc to increase five year survival. Reasons of why success not obtained as expected is further sought through Effect of IFNγ on PDL1 pathway and different NK cellular phenotypes is further analyzed besides role of NACT (neoadjunctive chemotherapy) on induction of immune response.

Keywords: Ovarian cancer; PD1/PDL1; Nivelumab; Olafarib; Cedinarib; IFNγ; NACT

Introduction

Over 75%of patients of ovarian cancer (OC) are in advanced stage III or IV disease on presentation [1,2], and OC remains the most lethal of gynaecological malignancies. Roughly 80%of patients with newly diagnosed ovarian cancer respond to platinum based chemotherapy. Even after proper debulking surgery and giving very effective first line chemotherapy around 70% of patients with advanced disease after obtaining remission will relapse finally [1,2]. Hence newer strategy for peritoneal dissemination is needed, other than the conventional chemotherapy. Tumor infiltrating lymphocytes (TIL) with antitumor potential exist in patients with cancer [3-6].

Role of PD1/PDL1

In a primary co culture system studies showed that TIL's from many patients with ovarian carcinoma secrete low to intermediate levels of IFNγ and have a limited proliferation in response to cognate peptides. The programmed cell death1 (PD1) is an inhibitory surface receptor which is expressed on T cells, B cells, natural killer cells (NK cells), monocytes and dendritic cells (DC) but not by resting T cells. PD1 binds to two ligands, Programmed cell death ligand1 (PDL1) and PDL2 known as BHI and B-7DC respectively [7,8]. Tumors can utilize the PD1 inhibitory pathway to silence the immune system [7]. The expression of PDL1 in tumors is inversely correlated with survival of patients. This indicates that although antitumor immunity is elicited against ovarian cancer, it is counterbalanced by immunosuppressive factors. In ovarian tumors myeloid cellsare one of the major determinants of immune suppression. In this is included tumor associated macrophage (TAM), immature tolerogenic dendritic cells and myeloid derived suppressor cells (MDSC) [9-18]. Additionally CD4+CD25+FoxP3 regulatory T cells (Treg) play a very important role in control of antitumor immune responses relying on PD1, PDL1 or CTL associated antigen 4 (CTLA4) to carry out these functions [19-23]. Duraiswamy et al. [24] showed the interaction between PD1 expressed on T cells and their ligands (PD1-PDL1:PD1-PDL2and PDL1:B7.1), expressed on other cells of the tumor microenvironment using a syngeneic orthotopic mouse model of epithelial ovarian cancer (ID8). Exhaustion of TIL correlated with the expression of PD1 ligands by tumor cells and tumor derived myeloid cells, including TAM, dendritic cells and MDSC. On comparing GVAX and PVAX Vaccination (consisting of irradiated ID8 cells expressing granulocyte macrophagecolony stimulating factor or FLT3 ligand) and co-stimulation by agonist α-4 –IBBor TLR9 and antibody mediated blockade of PD1 and PDL1 triggered rejection of ID8 tumors in 75%of tumor bearing mice. This therapeutic effect was associated with increased

proliferation and function of tumor antigen specific effect or CD8+Tcells inhibition of suppressive regulatory T cells and MDSC upregulation of effector T cell signaling molecules and generation of T memory precursor cells. Thus they concluded that PD1-PDL1 blockade enhances the amplitude of tumor immunity by reprogramming suppressive and stimulatory signals which gives more powerful cancer control [24].

Tumor Infiltrating NY-ESO1sp CD8+ Tcells and PD1/LAG3

Matsuzaki et al. [25] studied the cancer testis antigen NY-ESO1, commonly expressed in EOC, being the most immunogenic tumor antigens. They assessed the phenotype and function of NY-ESO-specific CD 8+Tcells derived from peripheral blood lymphocytes (PBLs), TIL'sand tumor associated lymphocytes (TAL's) of EOC patients with NY-ESO1expressing tumors, with or without humoral immunity to NY-ESO1. While NYESO1 specific CD8+Tcells were easily detected exvivo with tetramers in TIL's and TAL's of seropositive patients, they were only detected in PBLs following in vitro stimulation, As compared with PBL's tumor derived NYESO1-specific CD8+Tcells showed impaired effect or function, with preferred use of dominant Tcell receptor and enriched co-expression of inhibitory molecules LAG3 and PD1. Expression of LAG3 and PD1 on CD8+Tcells was up regulated by IL-10, IL16 (cytokines found in tumor as cites) and tumor derived antigen presenting cells. Functionally, CD8+LAG3+PD1+T cells were more impaired in IFNγ/TNFα production compared with LAG3+PD1- or LAG3-PD1- subsets. Dual blockade of LAG3and PD1 during T cell priming efficiently augmented proliferation and cytokine production by NYESO 1 specific CD8+T cells, which indicated that antitumor function of NY-ESO1 specific CD8+T cells could be improved potentially by improved by targeting these inhibitory receptors [25].

Role of VEGF Antibody inhibitors (Bevacizumab)

Peren et al. [26] examined the effects of bevacizumab on survival in women with ovarian cancer. They randomly examined the effects of bevacizumab on survival in women with ovarian cancer. They randomly assigned women with ovarian cancer to carboplatin (AUC 5 or6) and placlitaxel (175mg/m^2), given concurrently every 3 wks x5-6 cycles combined by additional 12 cycles or until progression of disease. Outcome measures included progress free survival (PFS), first analyzed per protocol and then updated and interim overall survival. A total of 1528 women from 11coutries were randomly assigned to one of the 2 treatment regimens. Their median age was57 yrs, 90% had EOC, 69% had a serous histologic type, 9% had high risk early stage disease, 30% were at high risk for progression and 70% had high stage III or IV cancer. Progression free survival restricted mean at 36 mths was 20.3, mths with standard therapy as compared to 21. 8mths with standard therapy plus bevacizumab (hazard ratio for progression or death with bevacizumab added) 0. 81; 95% Confidence Interval (0. 70 to 0. 94p=0. 04by log variant rate). Non proportional hazards were detected in (i.e. right effect was not consistent over time on the hazard function scale mths (p<0. 001) with a maximum effect on 12 mths coinciding with the end of planned bevacizumab treatment and diminishing by 29 wks. Bevacizumab was associated with more toxic effects (most often hypertension of gr 8% with chemotherapy alone. In the updated analysis progression free survival (restricted mean at 42mths was 22. 4mthswithout bevacizumab vs 24. 1mth without bevacizumab (p=0. 04by log rank test); in patients at high risk for progression, the benefit was >with Bevacizumab than without it, with progression free survival (restricted mean at 42mths of 14. 5mthswith standard therapy alone and 18. 1mth with bevacizumab added with respective median overall survival of 28. 8 mthsand 36. 6mths. Thus they concluded that bevacizumab improved PFS in women with ovarian cancer. The benefits with respect to both progression free survival and OS were greater in those who had a high risk for disease progression (ICON7 Controlled Trial. com noISRCTN91273375) [26].

There have been many reports on incorporating Bevacizumab in primary ovarian cancers and the OCEANS trial [27,28]. Lambreshts discussed some markers like neuropilin or VEGF receptor is forms to identify which patients may respond to bevacizumab [29]. Further Zuo et al. [30] conducted a metaanalysis and reported increased risks of cerebro vascular events in ovarian cancer patients treated with bevacizumab [30].

Oza et al. [31] reported the final results of ICON7 trial in 2015. ICON7 being an international phase III, open label, randomized trial undertaken at 263 centers in 11 countries across Europe, Canada, Australia and New Zealand. Eligible adult women with newly diagnosed ovarian cancer which was either high risk early stagedisease (International Federation of Gynecology and Obstetrics[FIGO]stage I-IIa, grade 3 or clear cell histology) or more advanced disease (FIGO stage IIb-IV) with an Eastern Cooperative Oncology Group performance status of 0-2, were enrolledand randomly assigned in a 1:1 ratio to standard chemotherapy (six 3wkly cycles of intravenous (iv) carboplatin [AUC 5 or 6]and paclitaxel 175mg/m (2) of body surface area) or the same chemotherapy regimen plus bevacizumab 7. 5mg/kg body wt IV every 3 wks given concurrently and continued with upto 12 further 3wkly cycles of maintenance therapy. Randomization was done by a minimization algorithm stratified by FIGO stage, residual disease, interval between surgery and chemotherapy and Gynecologic Cancer Inter Group. The primary end point was progression free survival; the study was also powered to detect a difference in overall survival. Analysis was by intention to treat.

They found between Dec 18, 2006 and Feb, 2009 1528 women were enrolled and randomly assigned to receive chemotherapy (n=764) or chemotherapy plus bevacizumab (n=764). Median follow up at the end of the trial on mar 31, 2013 was 48.9 months (IQR 26.6-56.2) at which point 714 patients had died (352 in chemotherapy grp and 362 in the bevacizumab grp). Their results thus showed evidence of non proportional

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hazards, so they used difference in restricted mean survival time as the primary estimate of the effect. No overall benefit of bevacizumab was recorded (restricted mean survival time 44. 6 mths [95%CI43. 2-45.9] in the standard chemotherapy grp vs 45. 5mths [44. 2-46.7] in the bevacizumab grp; logrank p=0.85). In an exploratory analysis of a predefined subgroup of 502 patients with poor prognosis disease 332 (66%) died (174 in the standard chemotherapy grp and 158 in bevacizumab grp), and a significant difference in overall survival was noted between women who received bevacizumab plus chemotherapy and those who received chemotherapy alone (restricted mean survival time 34. 5mths [95% CI32. 0-37. 0] with standard chemotherapy vs 39. 3mths [37.0-41.7] with bevacizumab; logrank p=0.03). However, in non-high risk patients the restricted mean survival did not differ significantly between the 2 treatment grps [49.7mths [95% CI 48.3-51.1]) in the standard chemotherapy grp vs 48. 4mths [47. 0-49.9] in the bevacizumab grp; p=0. 20. An updated analysis of PFS showed no difference between treatment groups. During extended follow-up, one further treatment related grade 3 event (gastrointestinal fistula in a bevacizumab-treated pt), 3grade 2 related events (cardiac failure, sarcoidosisand foot fracture, all in bevacizumab-treated patients), and one grade 1 treatment related event (vaginal hemorrhage in a patient treated with standard chemotherapy) were reported.

Thus they interpreted that addition of bevacizumab to platinum based therapy did not increase OS in the study population as a whole. However an OS benefit was recorded me poor -prognosis patients, which is concordant with the PFS result from ICON 7 and GOG2 18 and gives further evidence towards optimum use of bevacizumab in the treatment of ovarian cancer [31]. Poveda et al. [32] described the AURELIA trial on use of weekly paclitaxel, pegylated ribosomal doxorubicin or topectanin platinum resistant EOC [32].

Role of PARP (Olaparib)

Most patients undergo relapse and their responses to subsequent therapies are usually shortived [33-36]. Maintenance chemotherapy improves control of ovarian cancer [36] and further disease control is prolonged with bevacizumab and chemotherapy in patients getting first line treatment [31,37] and in those with platinum sensitive ovarian cancer which has relapsed [38]. Women having mutation in BRCA1, BRCA2 or both germline BRCA1/2, have an increased risk of ovarian cancers especially the most common types invasive high grade serous carcinomas [39].

Approximately 15%of EOC have a deficiency in homologous recombination repair due to mutations in BRCA1/2 [40, 41]. In high grade serous type tumor cells, may be deficient in homologous recombination (HR) in 50%of cases as a result of BRCA1 or defect in HR pathway that are independent of BRCA1/2 [42]. Silencing of genes or BRCA1/2 or their dysfunction leads to a BRCA ness phenotype similar to that resulting from inherent mutations in BRCA1/2. Microarray studies in serous EOC have found a BRCAness gene expression profile, which appears to correlate with responsiveness to both platinum based chemotherapy and poly adenosine diphosphate (ADP) -ribose polymerase (PARP) inhibitors [43, 44]. PARP plays an important role in repair of single stranded DNA breaks which cannot be repaired accurately in tumors with HR deficiency n [45,46], due to aberrant activation of low fidelity repair mediated by no homologous end joining b [47], a concept also called synthetic lethality [48]. Olaparib (AZD2281), as a potent oral PARP inhibitor that induces synthetic lethality in BRCA1/2deficient tumour cells [49,50]. Antitumor activity at doses which were not so toxic was observed in phase 1 and phases 2 mono-therapy studies involving patients with ovarian cancer who had BRCA1/2 mutations and 24%for those without such mutations. Ledermann et al. [51] conducted a randomized double blind, placebo controlled phase 2 study to examine the maintenance treatment with olaparib in patients with platinum sensitiv, relapsed, high grade serous EOC, who had got two or more platinum based regimens. Patients were randomly assigned to get olaparib at 400mg bd or placebo. The primary end point was progression free survival according to Response Evaluation Criteria in Solid tumor guidelines. Of the 265 patients who underwent randomization, 136 were assigned to the olaparib group and 129 to the placebo group. Progression free survival was significantly longer with olaparib than with placebo (median 8. 4mths vs 4. 8mths from randomization on completion of chemotherapy;hazard ratiofor progression or death, 0. 35;95% confidence interval[CI], 0. 25TO 0. 49;P<0. 001) . Subgroup analysisof progression free survival showed that regardless of subgroup, patients in the olaparib group had a lower risk of progression. Side effect were seen more in the olaparib group as compared to placebo therapy (by greater than 10% of patients) , were nausea (68%vs35%) , fatigue (48%vs35%) , vomiting (32vs14%) and anemia (17%vs5%) ;majority of side effects were grade 1 or 2. Overall survival (38%maturity i.e. 38%of patients had died) showed no significant difference between groups (hazard ratio with olaparib, 0. 94; 95%CI, 0. 63to1. 39; p=0. 75). Thus they concluded olaparib as maintenance treatment significantly improved PFS among patients with platinum sensitive, relapsed high grade serous EOC. Interim analysis showed no overall survival benefit. Toxicity profile of olaparib was similar to that in previous studies [51].

Further Ledermann et al. [52] in a retrospective analysis of maintenance monotherapy with olaparib presented data from second interim analysis of OS and a preplanned analysis of data by BRCA mutation from their randomized double blind , phase 2 study which assessed maintenance therapy with olaparib 400mgbd vs placebo in patients with platinum sensitive recurrent serous EOC, who had received 2or more platinum based regimens and who had a partial or complete response to their most recent platinum based regimen. Randomization was by an interactive voice response system, stratified by time to

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progression on penultimate platinum based regimen, response to the most recent platinum based regimen before randomization, and ethnic descent. The primary endpoint was PFS, analyzed by the overall population and by BRCA status. This study is registered with Clinical Trials gov numberNCT00753545. They found between aug2008 and feb 2010, 136 patients were assigned to olaparib and 129 to placebo. BRCA status was known for 131 (96%) patients in the olaparib group vs 123 (95%) in the placebo group, of whom 74 (56%) vs62 (50%) had a deleterious or suspected deleterious germline or tumor BRCA mutation. Of patient with a BRCA mutation, median PFSwas significantly longer in the olafarib group than in placebo group (11. 2mths, 95%CI8. 3-not calculable]vs 4. 3mths [3.0-5.4]; HR 0. 18[0.10-0.31; p<0. 0001), similar findings were noted for patients with wild type BRCA although difference between groups was lower (7. 4mths [5. 5-10. 3] vs5. 5mths [3. 7-5. 6]; HR 0. 54 [0.34-5.6]; HR [0.34-0.85]; P=0. 0075). At the second interim analysis OS (58%maturity), OS did not significantly differ between 2 groups [HR0. 88[95%CI0. 64-1. 21] P=0. 44); similar findings were noted in patients with mutated BRCA (HR0. 73[0. 45-1. 17] P=0. 19) And wild type BRCA (HR0. 99[0. 63-1. 55]; P=0. 96) . The most common grade 3 or worse side effects in olafarib group were fatigue (in 10 (7%) in olaparib group vs 4 (3%) in placebo group) and anaemia (seven [5%] vs one (<1%). Serious side effects were reported in 25 (18%) patients who got olaparib and 11 (9%) who received placebo. Tolerability was similar in patients with mutated BRCA and the overall population. Thus they concluded that patients with platinum sensitive recurrent serous EOC with a BRCA mutation have the greatest likelihood of benefitting from olaparib treatment [52].

Liu et al. [53] conducted a randomized open label phase 2 study to find the activity of olaparib monotherapy as compared to combination cediranib (an oral antiangiogenic with activity against VEGFR 1, 2 and 3) in women with ovarian cancer with measurable platinum sensitive, relapsed, high grade serous or endometrioid disease or those with deleterious germline BRCA1/2 mutations (gBRCAm). Patients were randomized using permuted blocks within stratum defined by gBRCA status and prior anti-angiogenic therapy to receive olaparib capsules 400mg twice daily. The primary endpoint was PFS analyzed under intention to treat. This trial is registered with Clinical Trial. gov, NCT01116648. 46/90 randomized patients received olaparib alone and 44 received olaparib/cediranib. Median PFS was significantly longer with olaparib/cediranib (17.7 vs 9. 0mths/HR 0. 42; p=0.005). Grade 3and 4adverse events were more common with olaparib/cediranib including fatigue (12vs5), diarrhea (10vs 0), and hypertension (18 vs 0). Subset analysis within stratum defined by BRCA ½ status demonstrated activity of olaparib/cediranib in both g BRCAm and gBRCAwt/u (wildtype unknown) patients. Significant improvement in PFS occurred in g BRCA wt/u women receiving olaparib/cediranib (16.5vs 5.7mths, p=0.008) with a smaller trend towards increased PFS in gBRCAm patients (19. 5vs 16. 5mths, p=0.16). Thus they interpreted that PFS with the combination olaparib/cediranib is significantly extended by 8.7 mths as compared to olefarib alone in recurrent platinum sensitive ovarian cancer. Because of the side effect profile further exploration on quality of life and patient reported outcomes to understand the effects of ongoing regimen to that of intermittent chemotherapy [53].

Role of Nivelumab (Anti PDL1 Antibody)

The microenvironment of atumor plays an important role in the development of cancer, along with its outcome and hence is an attractive target for planning therapeutic strategies. The microenvironment of epithelial ovarian cancer (EOC) has been under investigation. Heterogeneity in the tumor environment in patients with EOC and different immune cell populationshas been associated either negatively or positively with clinical prognosis including whole tumor infiltrating lymphocytes (TIL) [54], T regulatory cells [55,56], myeloid derived suppressor cells [57], tumor associated macrophages [58]. In the tumour a CD3+Tcell infiltrateare seen in the tumor islets which are intratumoral or intraepithelial Tcells In roughly 50%of EOC patients, while the rest 50%do not have intraepithelial T cells. Both prognosis and prediction of tumor outcome can be done on the basis of presence of intraepithelial T cells. In a metaanalysis conducted by Hwang et al. [59] of over 1800 cases it was revealed that the presence of high intraepithelial TIL is associated with both overall survival along with benefit from platinum based chemotherapies [59]. Presence of TIL indicates that the ovarian carcinomas are immunogenic. Many ovarian cancer antigens get recognized by T cells [60]. One expects that a part of this patient population would benefit from immune therapies aimed at reprogramming T cells against cancer cells.

TIL's express the negative costimulatory molecule known as programmed cell death1 (PD1) in human ovarian tumors, which is upregulated on Tcell activation and suppresses T cell effector functions, while various cell populations, which include cancer cells and tumor associated myeloid cells express its ligand PD-L1 [61-63]. Once PDL1 is expressed by tumors it is associated with reduced intraepithelial TIL'3and poor overall survival in EOC's [63]. In an immune competent murine model of EOC's PD1and PDL1 blockade=>eradication of tumors by reprogramming of the tumor microenvironment suggesting potential benefit from this PD1/PDL1 inhibition for patients with EOC.

In a large phase 1study which tested a human immunoglobulin G4 (IgG4) PDL1 blocking antibody 17 patients with ovarian cancer were treated with a 10mg/kgdose [64]. There was a partial response in 1patient and two patients experienced stabilization of disease for>24wks [64].

Hamanashi et al. [65] in a phase 2 trial studied 2 cohorts of PDL1 pathway in EOC patients with platinum and taxane resistant EOC's. They were treated with intravenous infusion of nivolumab (an anti-PD1antibody which blocks PD1 signaling). Two different doses 1or 3mg/kg every 2 weeks. On the basis of

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power calculation of the study if over one of 20 patients showed a response to nivolumab, the study would be considered positive and it would be worth considering a larger phase II or phase III trial. Other 20 patients in whom response could be evaluated the best overall survival was 15%, which included 2 patients who had a durable complete response (in the 3mg/kg cohort). Total disease control rate was 45%. Both completed responses happened at higher doses of 3mg/kg, which calls for a future phase III study at this dose. 6 additional patients had a stable disease as best response with an overall disease control rate of 45%. Low toxicity profiles of both doses were same as in earlier reports. Grade 3or 4 treatment related adverse events were seen in 8 (40%) of 20patients. Only 2 patients had severe side effects. Total objective responses were stable>24wk) in 5out of 6 patients. Results of Hamanashi et al. [65] are encouraging but overall response rate is low where reason needs to be found out.

Hamanshi et al. [65] analyzed PDL1 in archival tumor tissue. The results showed no correlation between PDL1 expression levels and benefits from nivolumab although patients withoutPDL1 expression had no definite benefit. This mimics previous findings which showed that high PDL1 expression is correlated with higher response rates however the negative and positive values of PDL1expression in tumours remains too low for acceptability to chronic treat ment. Previous studies in a mouse model of ovarian cancer depicted that PDL1 blockade needs a preexisting adaptive immunity in tumours and tumors without TIL's did not respond [66,67]. The same was seen in patients with melanoma who received PDL1 blockade monotherapy [67].

On one hand patients whose tumors lacked preexisting TIL's do not respond to PD1 blockade monotherapy or combination that focuses primarily in boosting T cell effector function. While conversely, most patients who respond possibly are those whose tumors were already infiltrated byrelevant tumor rejectingTIL's at the onset of therapy. Thus 45% overall disease control rate reported by Hamanishi et al. [65] agrees with the reported fraction of tumors which exhibit intraepithelial TIL in many studies.

Tumor types which have the biggest mutational burdens experience the best response rate of PD1 blocking antibodies [68].

Results of Haminishi encourage the development of combination which could offer positive interaction with PD1 blockade. Immune resistance pathway are likely distinct in ovarian tumors with preexisting intraepithelial TIL's vs tumours that lack these intraepithelial TL's which would require different combination therapy. Mechanism with TIL's which could also limit the efficacy of PD1 pathway are likely to operate in tumors with preexisting intraepithelial TIL's.

Other negative regulatory T cell receptors LAG3, TIM3, BTLA, CTLA4 etc may be implicated. Immunosuppressive soluble factors like interleukin, prostaglandin, TGFβ [69] high expression in the OC microenvitonment , could contribute to the suppression of T effector cells. Additionally negative metabolic receptors like indoleamine 2,3 dioxygenase [70] and L-arginase [71] can suppress cells through depletion of L-tryptophan and L-arginine respectively in EOC. Cotargeting of these resistance mechanisms may significanty enhance the antitumor efficacy of PD1/PDL1 blockade with expression of TIL's.

The mechanism underlying the paucity or absence of intraepithelial T cell infiltration in OC is likely to be heterogenous. Some ovarian tumors slow a molecular phenotype with gene signature which indicates proangiogenic and aromagenic reprogramming of the tumor microenvironment, which is associated with a low expression of immune activator genes and a low intraepithelial TIL'S [72]. Vascular barriers that prevent T cell homing have been shown in EOC [73,74] and they could be neutralized pharmacologically , by using combinations like adding bevacizumab to nivalumab. Other subset of EOC's exhibit a molecular phenotype which indicates cell multiplication, epithelial-mesenchymal transitionand activation of stem cell associated factors, that is associated with less expression of genes associated with stroma or inflammation in totality and thus show very little inflammatory infiltration [75]. In EOC's not having lymphocytic infiltration PD1/PDL1 blockade is not likely to be effective alone and combinations are needed to get tumor rejection adaptive immune response. Thus individual molecular phenotypes need to be targeted besides activation of tumor inflammation by innate immunity ligands like toll like receptor agonists, cytotoxic agents which induce immunogenic cell death, along with rational use of radiation could be important directions for future to activate tumor inflammation and immune rejection.

Role of IFNγ in PDL1 Expression

Immune evasion is an important aspect of cancer, it is important to understand the bases behind this to make effective therapeutic strategies. The group of Abiko and Hamanshi tried to find inhibitory immune molecules in ovarian cancer like ULBP2 (NKG2D) Ligand, COX1, COX2and PDL1 ligand system [75-77]. Among these PD1 showed the closest relation to poor prognosis in ovarian cancer [78]. By directly binding to its receptor PD1 transmits a signal which inhibits lymphocytic activation [79] Efficacy of anti-PDL1 antibodies in multiple cancer types is reported [66], and clinical trials in ovarian cancer are in progress. IFNγ-a cytokine known to be essential for innate and adaptive immunity, once adoptive immunity develops IFNγ secreted by activated effector T cells [80]. IFNγ upregulates MHC class Iand class II molecules and promotes antigen presentation on tumor cells [79]. By these functions IFNγ was expected to work as an antitumor agent, but in a trial tumor progression was promoted by IFNγin ovarian cancer patients [81]. The mechanism is not clear.

IFN also upregulates PDL1 expression on tumor cells [82]. In mouse melanoma models IFN secreted from CD8+Positive caused upregulation of PDL1 [83]. Also in mouse ovarian cancer

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model peritoneal dissemination models Abiko ei al showed IFN secreted from lymphocytes induces PDL1 on tumor cells [63]. To clarify in clinical studies ovarian cancer samples specially in peritoneal dissemination the relation between IFN and PDL1. Abiko et al. [84] examined the number of CD8+lymphocytes and PDL1 expression and tumor progression in mouse models under conditions of altering IFN-signal. They found that the number of CD8+ve cells in cancer stroma was very high in peritoneally disseminated tumors and w as strongly correlated with PDL1 expression on the tumor cells (p<0. 01) in mouse models depleting IFNGR (Interferon receptor1) resulted in lower peritoneal disseminated tumor growth and longer survival (p=0. 02). The injection of IFN into subcutaneous tumors reduced PDL1 expression and promoted tumor growth and PDL1 depletion completely abrogated tumor growth caused by IFN injection=0. 01). Thus they concluded interferon secreted by CD8+ lymphocytes up regulate PDL1 on ovarian cancer cells and promoted tumor growth. The lymphocyte infiltration of the IFNγ status maybe the k ey to effective antiPDL1therapy in ovarian cancer [84].

NK Cells and PDL1 expression

Presce et al. [85] studied if tumor NK cells can express PD1and analyzed their phenotypic /functional features. They carried out multiparametric cytofluorometric analysis of PD1+ NKcells and their functional characterization using granulation cytokine production and proliferation assays. They gave convincing evidence that PD1 is highly expressed ($PD1^{BRIGHT}$) on an NK cell subset detection in the peripheral blood of approximately 1/4thof healthy subjects. These donors are always serological positive for human CMV. PD1is expressed by $CD56^{dim}$ but not CD 56^{bright}NK cells characterized by the NKG2A-KIR+CD57 phenotype. Proportions of $PD1^{BRIGHT}$NK cells were higher in ascites of a cohort of patients with ovarian carcinoma, suggesting their possible induction/expansion in tumor microenvironment. Functional analysis revealed a decreased proliferative capability in response to cytokines low degranulation and impaired cytokine production and interaction with tumor targets. Thus they concluded that a subpopulation of human NK cells expressing high levels of PD1have been identified and characterized. These cells have the phenotype characteristics of fully mature NK cells and also increased in patients with ovarian carcinoma. They display low proliferative responses and impair the antitumor activity, which can be partially restored by antibody disruption of PD1/PDL1overaction [85].

Role of NACT in HGSC

Bohm et al. [86] tried to assess the effect of neoadjuvant chemotherapy (NACT) on immune activation in stage III or IV tuboovarian high grade serous carcinoma and its relationship to treatment response. Pre and post treatment omental biopsy samples were got in 54 patients undergoing platinum based NACT and 6 patients undergoing primary debulking surgery. They measured T cell density and phenotypic immune activation and markers of cancer related inflammation using IHC, F low cytometric electrochemiluminiscence assays and RNA sequencing and they related their findings to the histopathological treatment response. They found T cell activation on omental biopsies after NACT; CD4+T cells showed enhanced IFNγ production and antitumor Th1 gene signatures were increased. T cell activation was more pronounced with good response to NACT. The CD8+Tcell and CD45RO+ memory cell density in the tumor microenvironment was unchanged after NACT, but biopsies showing a good therapeutic response had significantly higher FoxP3+T regulatory cells. This finding was supported by a decrease in Treg cell gene signatures in post vs pre NACT samples, which was more pronounced in good responders. Plasma levels of pro-inflammatory cytokines decreased in all patients after NACT. However, a high proportion of T cells in biopsies expressed immune checkpoint molecules PD1and CTLA4, and PDL1 levels were significantly increased after NACT. Thus they concluded that NACT might enhance host immune responses, but this effect is tempered by high, increased levels of PD1, CTLA4 and PDL1. Sequential chemotherapy may improve disease control in advanced HGSC [86].

Conclusions

Thus EOC, one of the commonest killer of the gynecological malignancies as it gets detected late and in advanced stage, the need of the hour is improvement of both the neoadjunctive chemotherapy (like platinum and taxel based chemotherapy), which are also shown to influence the immune pathway and compounding them with newer immunotherapy's. The role of PD/PDL1 pathway is emphasized and how nivolumab, a monoclonal antibody may be utilized. Roles of IFNγ and specialized NK cells is discussed besides other factors of immune pathways which may have been responsible for not getting as good a response with nivolumab as expected theoretically. Utilization of combination therapies with Bevacizumab, PARP inhibitor olaparib, cedinarib is emphasized and more trials on nivolumab need to be assessed with these combinations vs. nivolumab alone. Thus one can expect better 5 year survival in this lethal cancer on making this diagnosis.

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