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Area tematica

Miscellanea

Titolo

Secondary effects analysis of the new immunotherapeutic agents used in oncology

Testo

Background: The approval of anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and anti-programmed cell death protein 1 (PD-1) antibodies resulted in significant improvements in disease outcomes for various cancers. PD-1 and CTLA-4 limit immune activation in physiological conditions and prevent autoimmunity, therefore inhibition of these receptors is associated with a wide range of autoimmune side effects. Interestingly, certain treatment-related auto-immune reactions have been shown to correlate with better prognosis suggesting a correlation between auto-immunity and anti-tumor immune responses. We conducted a retrospective analysis to explore this relation in an agnostic of cancer site population treated with checkpoint inhibitors.

Patients and methods: We conducted a retrospective analysis of patients with metastatic melanoma (MM), non-small cell lung cancer (NSCLC) and renal cell carcinoma (RCC) treated from September 2014 to February 2018 at our Institution (Fondazione Policlinico Universitario "A. Gemelli" - IRCCS) and exposed for the first time (in first or subsequent lines) to monotherapy with checkpoint inhibitor (Ipilimumab or Nivolumab or Pembrolizumab). The aim was to correlate the auto-immune adverse events (AE) with progression free survival (PFS). A multivariate analysis was performed with prognostic factor which could limit this unconventional analysis (line of therapy: 1 vs >1, gender: male vs female, cancer site: melanoma vs non melanoma, immune therapy: anti-PD-1 vs anti-CTLA-4).

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Conclusions: Despite the limitation of the retrospective nature of this study and the possible bias due to the peculiar selection of patient, our data showed an interesting association between auto-immune AE and outcomes of checkpoint inhibitor therapy in an agnostic of cancer site population

Parole Chiave

1. Immunotherapy
2. Side effects
3. Increased PFS

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Il Suo lavoro è stato contrassegnato con il numero " **S38** " e verrà pubblicato nella Sessione **" Miscellanea "**.

La suddetta pubblicazione è strettamente subordinata al pagamento della quota d'iscrizione di almeno uno degli autori del lavoro.

RingraziandoLa per il fattivo contributo offerto al Congresso, cogliamo l'occasione per inviarLe i nostri più distinti saluti.

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Plenary Session

01*

COMPREHENSIVE BIOMARKER ANALYSES AND UPDATED RESULTS OF PURE-01 STUDY: NEOADJUVANT PEMBROLIZUMAB (PEMBRO) IN MUSCLE-INVASIVE UROTHELIAL BLADDER CARCINOMA (MIBC)

Raggi D.[1], Briganti A.[2], Luciano' R.[2], Colecchia M.[1], Massa S.[1], Giannatempo P.[1], Colombo R.[2], Gallina A.[2], Mortarini R.[1], Montorsi F.[2], Madison R.[3], Ali S.[3], Ross J.[3], Chung J.[3], Anichini A.[1] and Necchi A.[1]

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Background: PURE-01 (NCT02736266) is a single-arm, phase 2 study of Pembro preceding radical cystectomy in MIBC. Updated results and exploratory biomarker analyses are presented.
Methods: 71 patients (pts) will be enrolled, with cT⩽3bN0 MIBC, regardless of cisplatin eligibility. Pembro is given 200mg q3w x3 cycles. Pathologic complete response (pT0) in ITT population is the primary endpoint (EP). The H_1 is pT0 ⩾25%, H_0 pT0⩽15%. 15/71 pT0 are required. Biomarker analyses include: IHC PD-L1 combined positive score (CPS, Dako 22C3), hybrid-capture based comprehensive genomic profiling (CGP, FoundationONE), and expression of a 22-gene "T-cell inflamed" signature via quantitative PCR (qPCR).
Results: As of 05/2018, 65 pts have been enrolled and all underwent CGP from TURB samples: 42% showed DDR genomic alterations (GA). Median CPS was 21%. CPS and qPCR showed a significant correlation (r=0.71, p<0.0001), whereas CPS did not correlate with neither tumor mutational burden (TMB) nor DDR-GA (R=-0.16). 37 pts are evaluable for the primary endpoint. With 15 (40.5%) pT0 responses, the study has already achieved its PE.

RB1 and *PBRM1* GA were significantly associated with pT0 (p=0.014 and p=0.007). pT0 responses were obtained in 10 (52.6%) pts with CPS⩾21% and, most noteworthy, in 13 (61.9%) with DDR or *RB1* GA. 8/8 pts (100%) with DDR/*RB1* GA and CPS⩾21% achieved pT0. The 22 gene T-cell inflamed signature also significantly discriminated pT0 from non-pT0 pts (p=0.0032).

17 pts had matched pre-post Pembro tumor samples analyzed, showing a mean of 51.9% shared GA. Concordant increases in gene expression by qPCR, observed in post- vs pre-Pembro lesions, from at least 5/7 non responding patients, were consistent with promotion of adaptive immunity (*IFN-g*, *CXCL9*, *CXCR6*, *CD27*, *GZMB*), being counteracted by strong adaptive resistance mechanisms (*CD274*, *PDCD1*, *CD276*, *PDCD1LG2*, *IDO1*).
Conclusion: Pembro has already exceeded the pT0 responses required in this study. Many new observations and the immune-genomic features interplay may contribute identifying those pts who might deserve a bladder-sparing approach. Full results on the entire dataset will be presented.

02*

CHEMOTHERAPY PLUS OR MINUS BEVACIZUMAB FOR PLATINUM-SENSITIVE OVARIAN CANCER PATIENTS RECURRING AFTER A BEVACIZUMAB CONTAINING FIRST LINE. THE RANDOMIZED PHASE 3 TRIAL MITO16B -MANGO OV2B - ENGOT OV17

Daniele G.[1], Lorusso D.[2], Joly F.[3], Gallo C.[4], Colombo N.[5], Sessa C.[6], Bamias A.[7], Pisano C.[8], Selle F.[9], Zaccarelli E.[5], Scambia G.[10], Pautier P.[11], Nicoletto M.O.[12], De Giorgi U.[13], Dubot C.[14], Bologna A.[15], Orditura M.[4], Ray-Coquard I.[16], Perrone F.[1] and Pignata S.[17]

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Background: Bevacizumab (BEV) is approved in recurrent ovarian cancer (rOC) for patients not previously

Backgroung: Clinical research have given attention to the sexual disorders of female and young patients. Little is know instead of the sexual-affective dimension in elderly males longterm cancer patients.
Material and methods: this is a monocentric and monophasic study; 30 longterm elderly patients with different primivitivities were interviewed. The questionnaire administered were the IOQ and another that evacuate the personal and clinical data collection and the sexual-affective patients dimension.
Results: 17 men and 13 women were recruited. Averege age 68.06 (62-87); the average spent time from diagnosis exceeds 10 years (range 5-26). The 66.6% were married. The 56.6 % of respondents claimed that the disease has changed the intimacy with the partner (item 25 IOQ); 43.4% reported a significant decrease in sex desire, after the cancer diagnosis (item 4 QI) and 50% reported no sexual activity (item 3 QI). None of them searched for a medical supportive treatment (item 6 QI) and only 10% received psychological counseling (item 10 QI).
Conslusions: The results suggest that elderly males cancer patients, as the female and yonger patients, have a sexual-affective dimension that is compromised, even after years from diagnosis, by disease and its treatment. At the same time they highlight the oncologist lack of attention to this need.

S37

CAN SYSTEMIC THERAPY INCREASE THE TOXICITY AND RATE OF RADIONECROSIS IN STEREOTACTIC RADIOSURGERY FOR BRAIN METASTASES?

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Introduction: Stereotactic Radiosurgery (SRS) is an effective treatment for brain metastases (BM) and may be generally safe. The relative risk of toxicity in patients treated with combination target therapy/immunotherapy and SRS has not been well-defined.
Methods and Materials: We analyzed all patients treated between 2010 and 2017 at our institution with SRS for BMs with or without concurrent systemic therapy. We evaluated in this cohort of patients the haematological and neurological toxicity, brain progression free survival and overall survival, stratifiyng patients for yes / no systemic therapy and type of systemic therapy.
Results: Data on 45 patients were obtained. Median age at diagnosis of BM was 66 years (range, 37-90 yrs). At the time of initial presentation of BMs, the majority of patients had ECOG perfomance status of 0-2. The most common primary tumors were lung, breast, melanoma and kidney. Sixty percent of SRS treatments were delivered concurrently with systemic therapy, of which 56% were with conventional chemotherapy and 44% with targeted and immunotherapy agents. Patients were divided in two groups: SRS alone and SRS/systemic therapy. No differences between the two groups of patients in terms of clinical and treatments characteristics were found. Median follow up was 10 months (range, 1-65 months) from the time of SRS. Myelosuppression was minimal after treatment, with 9% grade 2-4 toxicity; grade $>$ 2neurological symptoms were reported in 11% of patients, with one grade 5 neurological toxicity. Histologically confirmed radionecrosis was reported in 2 patients (one in SRS alone and one in SRS-systemic therapy group) and radiologically suspected radionecrosis in 2 patients both in the group of concurrent therapy (one with chemotherapy and one with target therapy). No difference in haematological (p=0.79) and neurological (p=0.96). Median brain PFS was 12.1 months, without any significant difference between the two group (p=0.49). To date 29 patients have died, of which 3 for brain progression, 13 for systemic progression and two for both systemic and brain progression. Nine patients were died for no tumor related causes and 2 patients for unknown causes. Median overall survival for entire group was 8.13 months without any difference between the two group of patients. (p=0.369).
Conclusions: Systemic therapy can be safely given concurrently with SRS for BMs without increase of neurological toxicity and radionecrosis risk.

S38

SECONDARY EFFECTS ANALYSIS OF THE NEW IMMUNOTHERAPEUTIC AGENTS USED IN ONCOLOGY

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Background: The approval of anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and anti-programmed cell death protein 1 (PD-1) antibodies resulted in significant improvements in disease outcomes for various cancers. PD-1 and CTLA-4 limit immune activation in physiological conditions and prevent autoimmunity, therefore inhibition of these receptors is associated with a wide range of autoimmune side effects. Interestingly, certain treatment-related auto-immune reactions have been shown to correlate with better prognosis suggesting a correlation between auto-immunity and anti-tumor immune responses. We conducted a retrospective analysis to

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S39

CANCER RISK AFTER EXPOSURE TO PERFLUOROALKYL SUBSTANCES (PFAS): EVIDENCE FROM LITERATURE

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Background: From the literature we know that perfluoroalkyl substances (PFAS) are persistent environmental contaminants. However, their metabolism and distribution in humans tissues are not well studied and few data have documented the accumulation of PFAS in specific issues, such as lung, kidney, brain and bone. Recently, in a monograph, the International Agency for Research on Cancer classified PFOA as "possibly carcinogenic to humans" (Group 2B). In the absence of clear data that can demonstrate the association between PFAS and cancer, it might be interesting to compare the evidence in the literature about the possibile association between PFAS and the different types of human cancer.

Table 1. The relantionship between PFAS exposure and the different types of human cancer in the considered studies.

Cancer	**Mastrantonio et al.** Eur J Public Health2018;28:180-5.	**Vieira et al.** Environ Health Perspect2013;121:1318-23.	**Barry et al.** Eur J Public Health2018;28:180-5.
Bladder	+/−	−	−
Brain	NE	−	+/−
Cervical	NE	NE	−
Colon/rectum	NE	−	−
Esophagus	NE	NE	−
Female breast	+	+/−	−
Kidney	+/−	+	+/−
Leukemia	+/−	−	+/−
Liver	−	−	−
Lung	NE	−	−
Lymphoma	−	+/−	+/−
Melanoma of the skin	NE	−	−
Multiple myeloma	NE	−	−
Oral	NE	NE	−
Ovary	+/−	+	−
Pancreatic	−	−	−
Prostate	−	+/−	−
Soft tissue	NE	NE	−
Stomach	NE	NE	−
Testicular	−	+	+
Tyroid	NE	−	+/−
Uterus	NE	−	+/−

Legend: NE= not evaluated; += statistically significant; +/−= not statistically significant but with positive trend; −= not statistically significant.