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Conference Review

Leadership in immuno-oncology network 2 (LION:2) immunotherapy oncology - A present status

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The constant barrage of immuno-oncology therapeutics in the past few years necessitated a collaborative effort by major oncology societies and noted oncology professionals in the country to join hands and form leadership immuno-oncology network (LION). In the second installment of the LION master-class, which was held in Delhi this year, this endeavor continued to enlighten and educate hundreds of students, delegates, and professionals from all over India. 132 medical oncologists from all over the country actively contributed to the discussions. The essence of the educational event was, learning from each other's experience as well as reviewing and analyzing the ever-increasing body of evidence pertaining the subject in a systematic manner. This year the initiative was spearheaded by Dr. Vineet Talwar and Dr. Ankur Bahl as program coordinators for the meeting.

Oncology heavily relies on biomarkers, especially with regard to targeted therapies. But when it comes to immune therapeutics such as PD-L1 and CTLA-4 blockers, our biomarker armamentarium, is but an enigma of some sort. The nuts and bolts were tightened around the molecular perspective of immune-oncology in the panel discussion moderated by Dr. Anurag Mehta from RGCI. PD-L1 cutoffs and platforms were reviewed, as was the blue print study. He opined that although the phase 2 of Blueprint study[1] comparing 4 different PD-L1 clones (22C3, SP142, SP263, and 28-8) presented at WCLC 2019 showed concordance among three of the clones, except SP142 which stains lower percentage of tumor cells in general, it would be too early to make strong recommendations regarding using these clones interchangeably based on this small dataset. The panel comprising both molecular and medical oncologists reiterated his point of view and suggested that we stick to the recommended cutoffs of PD-L1 which are drug-specific and clone specific. For pembrolizumab, a cutoff of 1% is recommended in the second line for monotherapy[2] while for first-line monotherapy a cutoff of 50% is suggested using the 22C3 clone.[3] Nivolumab can be used in second line irrespective of PD-L1 expression.[4,5] When using in combination with chemotherapy, pembrolizumab can be used at any level of PD-L1 expression.[6,7] Interestingly, there are no data on the comparison of pembrolizumab alone versus Pembrolizumab + chemotherapy although we have a sizable dataset for Pembrolizumab + Chemotherapy versus chemotherapy alone. Hence, while monotherapy with pembrolizumab may be enough for patients with >50% PD-L1 expression, we still do not have a clear answer on whether adding chemotherapy to ICB even in this subset will be advantageous or not.

The discussion of total mutation burden was particularly informative. Tumor mutational burden (TMB) is defined as the number of somatic, coding, base substitutions, and short indels per megabase of genome examined.[8] Although whole exome sequencing was the initial methodology for TMB analysis in checkmate –026,[9] subsequent trials have efficiently used targeted gene panels (e.g., FoundationOneCDx and MSK-IMPACT) to calculate TMB.[10,11]. The consensus was that targeted NGS can be used for TMB calculation using a validated and standardized platform. The moderator also emphasized that an average 1.2 MB (Megabase pairs) of data and a minimum of 0.5 MB of data should be obtained for TMB analysis. Furthermore, germline mutation analysis changes the TMB calculation and improves the accuracy of the result.

All in all, the consensus was there exists no truly reliable biomarker for immunotherapy response. Future approaches may combine PD-L1, TMB, TILS, neoantigens, MSI status, gut microbiome, and mutations positively correlating with responses such as P53, JAK3, POLE, POLD1, specific mutations in SMARCA4, and dampening mutations such as EGFR, MDM2, MDM4, and DNMT3A.[12-14] It was also emphasized

that for renal cell carcinoma, Merkel cell carcinoma, melanoma, and Hodgkin lymphoma no biomarkers are required.

The discussion on medicolegal aspects of immuno-oncology was moderated by Professor Purvish Parikh. A plethora of queries was raised by the audience and the panel, and there were some important take-home messages from the session. There was a reasonable consensus on using package inserts as the legally most valid information resource for patients. The moderator emphasized that although drug approvals by local authorities carry more weightage than guidelines, we must use scientific information in a balanced manner and make sure we act in the best interest of the patient. The model of shared decision making was encouraged. Using technology for passing on information to patients and families through Bonafide websites, online resources and apps should be incorporated for a smoother patient experience and as an important measure to bridge gaps in communication.

Some less often discussed tumors were given their due this year. For gastric cancer patients benefit is probably more with increasing PD-L1 expression though PD-L1, independent activity has been demonstrated in small datasets.[15-17] For hepatocellular carcinoma, there was a consensus regarding using ICBs as a second line for eligible patients as per CHECKMATE 040. ECOG-PS and sorafenib exposure were important determinants of survival though ICBs benefitted all subsets in a similar fashion.[18]

For MSI-H colorectal cancer a 50–60% response rate can be achieved with ICB monotherapy or combos of PD-L1 and CTLA-4 blockers.[19,20] KEYNOTE 177 is set to answer whether pembrolizumab monotherapy can trump physician's choice of chemotherapy in this subset of patients.[21] There was a consensus on using ICBs in the post-5-FU, oxaliplatin, and irinotecan patients only for now and keeping the use of ICBs in the earlier line reserved in select situations only. However it seems likely that in future chemoimmunotherapeutic strategies in combination with antiangiogenic drugs or radiation to enhance antigenicity may assume more importance. Similarly, the abscopal effect of radiation in combination with immunotherapy may assume more importance in future.[22]

Hematoncology is not untouched from the effect of immunotherapeutics. Professor Dr. Atul Sharma analyzed the ICB data for hematolymphoid neoplasms. He correctly pointed out that, though very encouraging activity of nivolumab and pembrolizumab has been demonstrated in Hodgkin lymphoma, natural killer T cell Lymphoma, acute myeloid leukemia, and myelodysplastic syndromes, leading to regulatory approvals for Hodgkin lymphoma at least, the therapeutic armamentarium is much larger for hematology oncology in terms of targeted therapies and extends much beyond immune-oncology.[23] Autologous and allogenic stem cell transplants still seem more cost-effective and viable in the Indian context. Furthermore, targeted options and monoclonal antibodies are more viable in most situations in hematology oncology. Chimeric antigen receptors-T cells were briefly touched on; it was felt that these were beyond the reach of most of our patients due to logistic constraints, although there was a general wave of excitement in this regard among the attendees.

Immuno-oncology has transformed uro-oncology in the eyes of many, but Dr. Alok Gupta, who summarized the urologic immuno-oncology session, brought out some very significant observations. One, though response rates have shown an improvement in Javelin 101 with IO+TKI and IO + Bev in IMMOTION −151, we have not gone beyond improving PFS,[24,25] only CHECKMATE 214 could show OS with Nivo/Ipi in intermediate/high-risk RCC.[26] The panel was not particularly impressed with IO data for unresectable urinary bladder cancer, but did consider IO as a viable option in PDL1 expressing tumors in platinum refractory or platinum ineligible population.

Controlled enthusiasm was the term which Dr. Anita Ramesh preferred to use for ICBs in head and neck cancer. With the evident OS benefit, ICBs have truly transformed care for metastatic head and neck cancer patients. With a minimum follow-up of 11.4 months, overall survival for the entire study population in CHECKMATE-141 was significantly longer in patients treated with nivolumab (median 7.7 vs. 5.1 months, 1-year survival rate 34.0 vs. 19.7%, hazard ratios 0.71, 95% confidence interval 0.55–0.90). The objective response rate was also increased with nivolumab (13.3 vs. 5.8%).[27]

Response assessment when using ICBs has always been looked on as a challenge. This point of view was put to thorough scrutiny by Dr. Vamshi Krishna and Dr. Senthil Rajappa. After the session, it was quite apparent that the immune response criteria such as iRECIST and irRECIST are more of research tools rather than sacrosanct concrete guides for therapeutic decision making. Consensus was that we were putting too much emphasis on pseudoprogression, and pseudoprogression is a rare phenomenon on except in select situations like melanoma. Although it is wise to know these criteria, clinical stability is the key. Any progression should be confirmed with scan 4–8 weeks later. If the patient is clinically doing well, the consensus was to scan after at least 8–12 weeks of therapy.[28,29]

Clinical stability should be defined as, noworsening of ECOG-PS, no disease-related symptoms, and no requirement of intensified symptom control.

Hyperprogression is a phenomenon where a >50% increase in target lesions is documented within 2 months of treatment, and we must identify these patients in time. The bottom line of the discussion was, immune response assessment criteria are still not a validated clinical tool.[30]

Other important general recommendations to improve outcomes of patients on ICBs made during the subsequent discussion were to avoid steroids, antibiotics, and proton pump inhibitors during ICB use. Furthermore, premedications should not be used with IO drugs with exception of Avelumab.[31] The consensus was also to avoid using ICBs in patients with a poor ECOG-PS.

Toxicity concerns were summarized by Dr. Sewanti Limaye and Dr. UllasBatra, who advised oncologists to check CTCAE grades every time they encounter toxicities in patients on IO drugs. The moderators gathered from the very interactive session that thinking steroids early in suspicious and life-threatening situations is the key to saving lives, and also encouraged interaction and communication with allied branches such as pulmonology, endocrinology, critical care, gastroenterology, and rheumatology while managing these toxicities. The consensus was to sensitize allied departments with respect to ICB toxicities and be an active member of the treating team.

Dr. Shyam Aggarwal advised a thorough history and organ function assessment before considering ICBs. The consensus was to perform complete blood counts, liver, kidney, and thyroid function tests and assess cardiac function before initiation of ICBs as basic work up. Autoimmune work up and other investigations may be considered on a case to case basis.

To conclude, the meeting was an important step forward in providing India specific evidence-based recommendations regarding IO drugs and was able to successfully harness the collective experience of the nation's oncology community in the context of immuno-oncology. LION resolves to continue empowering oncologists with such open knowledge sharing platforms in future.

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