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ESMO 2023: Management of novel treatments' toxicities

Industry Overview

Toxicity management is key to successful treatment

At ESMO 2023, we spotlighted on "Management of Novel Treatments' Toxicities" due to recent advances and growing interests in new treatment modalities, including ADCs, IO combo, and cell therapy. Our key takeaways are provided below.

ADC: A learning curve for prescribers to manage toxicities

ADCs are an emerging and rapidly expanding therapeutic class that are transforming the treatment paradigm across a broad range of cancer indications, including lung, breast, and bladder cancers. That said, ADCs come with their own unique set of toxicity profiles that need to be managed carefully. At a high level, the structure of the ADCs and their components (antibody specificity, linker characteristics, and nature of the chemo payload) are the main determinants of their efficacy/toxicity profiles. Indeed, the determinants of toxicities are due to 1) system drug release before reaching the target (toxicity according to systemic effect of the chemo payload), 2) expression of the target antigen by normal tissue, 3) uptake of ADCs and conjugates clearance, and 4) bystander effect. As such, changing one component can dramatically alter an ADC's toxicity profile (e.g., GI side effects vs. ILD/pneumonitis) or its efficacy/target indication (HER2+ vs. HER2- breast cancer). Overall, while there's no one-size fit all approach given the unique toxicity profile associated with each ADC, the experts believe that there'll be a learning curve for prescribers but expect the overall risks to come down in the real-world setting.

IO-based tox management needs individualized approach

Immune checkpoint inhibitors (e.g., PD-1, CTLA-4) have transformed cancer treatment paradigm for nearly all solid tumor treatments over the last 10 years. As such, their toxicity profiles are generally well understood. That said, the field has moved into combination approach (IO + targeted therapy) to deliver better efficacy but with a higher risk of additive toxicities. At a high level, experts believe that managing IO-based combination toxicities require individualized approach through interdisciplinary collaborative managed care given the variety of adverse events. With that said, there are three basic treatment principal and observations: 1) antibiotics should be avoided as their use are associated with worse OS/PFS, 2) use of concomitant steroids have no impact on survival, 3) and varying treatment cycles and temporary treatment cessation can help managing tox level while maintaining a similar level of survival benefit.

CAR-T's tox is severe and needs to be managed carefully

CAR-Ts have revolutionized the ways in treating hematologic cancer (e.g., DLBCL), curing patients with one single treatment course. At the same time, patients are subject to a unique set of toxicities, including CRS and ICANS, which can result in organ dysfunction, seizures, coma, and death. Interestingly, there's no patient exclusion criteria for CAR-Ts, including age, history of malignancy, prior treatments including stem cell transplants, immunosuppressive therapy, or CNS disease; only active infection is a contraindication. Overall, experts recommend steroids premedication and step-up dosing as way to manage the adverse events. That said, experts noted bispecifics, given their favorable efficacy and safety profiles, should be considered as additional options for the patients.

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Abbreviations:
IO: immunotherapy
OS: Overall survival
PFS: Progression-free survival
ADC: antibody drug conjugate
TROP2: trophoblast cell-surface antigen 2
1L: first line
EGFR: epidermal growth factor receptor
NSCLC: non-small cell lung cancer
CRS: cytokine release syndrome
ICANS: neurotoxicity
CNS: central nervous system
CAR-T: chimeric antigen receptor
ESMO: European Society for Medical Oncology
HER2: Human epidermal growth factor receptor 2
ILD: Interstitial lung disease
DLBCL: Diffuse large B-cell lymphoma
CTLA-4: Cytotoxic T-lymphocyte-associated protein 4
PD-1: Programmed cell death protein 1

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