IMMUNOTHERAPY

Insights into the risk of fatal AEs with ICIs

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Immune-checkpoint inhibitors (ICIs) have transformative effects in a subset of patients, across a range of cancer types. Nevertheless, all patients who receive these agents are at risk of the associated adverse events (AEs), which are diverse, distinct from those of anticancer treatments without a predominant immune mechanism of action and can be fatal. Data on the toxicities of ICIs have mostly come from reports of single clinical trials, providing limited insight into their true incidence. Now, a comprehensive systematic review of the available data provides new insights into the safety of ICIs, with a focus on rare fatal AEs.

"The characteristics of fatal toxicities were not previously well understood given that <10 fatalities have been reported in any single manuscript," explains Douglas B. Johnson, who coordinated the study. To overcome this limitation, Johnson and colleagues reviewed global data collected from published international clinical trials of ICIs, from the WHO Vigilyze pharmacovigilance database or at seven large academic medical centres.

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"We were struck by not only the uncommon nature of serious toxicities but also the diversity of the organs affected, as well as the early onset after starting treatment," Johnson states. "Fatal immune-related AEs were also uncommon, but differed somewhat by treatment regimen (occurring in 0.3–1.3% of treated patients) and also affected a variety of organs," he adds.

Of 31,059 individual ICI-related case reports entered in the Vigilyze database between 2009 and January 2018, 613 AEs (1.97%) were fatal. Anti-CTLA-4 antibodies were linked to 193 of these deaths, primarily owing to colitis (70%), followed by hepatitis (16%) and pneumonitis (8%). The 333 deaths linked to treatment with PD-1 or anti-PD-L1 antibodies were predominantly caused by pneumonitis (35%), hepatitis (22%) or neurotoxicities (15%). Combined inhibition of CTLA-4 and PD-1 or PD-L1 seems to exacerbate some of the toxicities of the latter agents, with 37% and 25% of deaths caused by colitis and myocarditis, respectively (versus 17% and 8% with PD-1 or PD-L1 inhibition alone). By contrast, the proportions of fatal AEs attributed to pneumonitis or neurotoxicity were lower with the combination (14% and 8%, respectively). Fatal AEs tended to occur early during treatment (median time to onset was 40 days with either monotherapy and 14.5 days with combination therapy). Myocarditis warrants particular concern because ~40% of reported cases were fatal, compared with 2–17% for other toxicities.

These data are broadly in keeping with those from 3,545 patients treated with ICIs at the academic centres. In this data set, the overall fatality rate was 0.6%, attributed primarily to myocarditis, neurotoxicity, colitis or hepatitis. The median times from treatment initiation to symptom onset and from symptom onset to death were 15 and 32 days, respectively.

Similarly, a meta-analysis of data from 112 published trials, comprising 19,217 patients, revealed fatal AE rates of 0.36% (PD-1 inhibition), 0.38% (PD-L1 inhibition), 1.08% (CTLA-4 inhibition) and 1.23% (PD-1 or PD-L1 plus CTLA-4 inhibition). The profile of fatal AEs was generally comparable to that determined using Vigilyze, although with a notably greater proportion of infectious causes.

"Clinicians and patients should be aware of the potentially serious nature of these toxicities; physicians should have a low threshold for suspicion of immune-related toxicities in patients receiving ICIs and treat them promptly with steroids," Johnson advises. The data underscore the need for particularly close vigilance in the first months of treatment.

At present, determining which patients will respond to ICIs and which are at risk of AEs remains a game of chance. "Developing predictors of severe toxicities, more effective management approaches for serious events and more selective anticancer immunotherapies are key unmet needs," says Johnson. "We are currently performing in-depth molecular studies to try and understand the mechanisms of severe toxicities," he concludes. Indeed, understanding the biology of AEs will be crucial to improving the therapeutic index of current and future immunotherapies.

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