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COVID-19 Rapid Letter

The importance of IL-6 blockade beyond the COVID-19 pandemic: Consideration for cancer care ☆

The novel human Coronavirus (SARS-CoV-2), which outbroke in Wuhan (China) in late 2019, is now responsible for the pandemic diffusion of COVID-19 [1–3]. Researchers are working on the validation of effective protocols, including antiviral therapies and vaccines [4]. Case-fatality rate seems correlated with virally-driven hyperinflammation [4,5]. In this sense, recent data suggest a crucial role for cytokines release syndrome (CRS) and human interleukin-6 (IL-6) levels as fatality predictors [4,5]. In this regard, tocilizumab, an IL-6 receptor inhibitor, is currently under investigation for patients with severe COVID-19 and elevated IL-6 levels, in order to counteract the pro-inflammatory CRS. Randomized trials have been approved in China and Europe to explore this hypothesis [6,7].

Blocking IL-6 has been proved beneficial in inflammatory diseases, as rheumatoid arthritis [8].

Nevertheless, elevated levels of IL-6 may also play a role in cancer [9].

With respect to cancer pathogenesis, overexpressed IL-6 stimulates the JAK/STAT3 signaling hyperactivation, often associated with poor patients' outcomes [9].

The aberrant hyperactivation of the IL-6/JAK/STAT3 pathway impacts on tumor microenvironment via two mechanisms:

- acting as a driver of tumor cell proliferation and scattering capacity
- suppressing the antitumor immune-response [9].

Specifically, STAT3 hyperactivation has been linked with chemotherapy and radiotherapy (RT) resistance, given its critical role in the interaction between tumor-associated macrophages and tumor cells [10]. Thus, targeting IL-6 may enhance tumor control [9].

The relation between IL-6 and RT has been investigated in head and neck cancer (HNC) [10,11].

Interestingly, in a series of 26 HNC patients, serum levels of pro-inflammatory markers, as IL-6, were found to be increased after RT and chemo-radiotherapy [11]. Thus, paradoxically, cancer treatments may favor a tumor-promoting pro-inflammatory microenvironment [11].

Accordingly, Matsuoka et al. hypothesized improved treatment response and survival in oral squamous cell carcinoma patients, when adding tocilizumab to RT, given its capacity to limit the IL-6 effect in reducing radiation-induced DNA damage [10].

The potential beneficial synergism on tumor microenvironment when combining RT and IL-6 blockade is being currently explored in specific oncological settings, as in pretreated advanced pancreatic cancer (PC) [12]. Patients enrolled within the Danish phase II TRIPPLE-R trial are planned to receive a 15 Gy single fraction of stereotactic body RT (SBRT), nivolumab, ipilimumab and tocilizumab [12].

The rationale is based on preclinical data showing that PC may act via multiple immune-evasion patterns [13].

Therefore, immune-checkpoint inhibitors combination is proposed to overcome the tumor "immune-escape" mechanism to potentially improve outcomes [12]. The addition of tocilizumab is aimed at limiting cancer progression, by counteracting the hyperactivation of the IL-6/JAK/STAT3 pathway [9].

As an immunological adjuvant strategy to increase antigen-release, patients will receive SBRT [12,14].

Of interest, the same 3-drug combination is being evaluated within an ongoing phase II trial enrolling unresectable stage III–IV melanoma patients [15].

To conclude, this pandemic highlighted the importance of the IL-6 pathway within the CRS, observed during severe COVID-19. This led the Scientific Community to focus on the IL-6 blockade clinical potential. Since IL-6 is overexpressed in different cancers, promoting tumor progression, the present times may represent a boost to further investigate the combination of radiotherapy and therapies targeting the IL-6 pathway.

Conflict of interest

No.

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