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PEER-REVIEW REPORT

Name of journal: World Journal of Clinical Oncology

Manuscript NO: 60532

Title: Systemic Adverse Effects and Toxicities Associated With Immunotherapy: A Review

Reviewer's code: 01851506
Position: Peer Reviewer
Academic degree: PhD

Professional title: Professor

Reviewer's Country/Territory: Japan

Author's Country/Territory: United States

Manuscript submission date: 2020-11-03

Reviewer chosen by: Jin-Lei Wang

Reviewer accepted review: 2020-12-28 10:34

Reviewer performed review: 2020-12-30 01:02

Review time: 1 Day and 14 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

This review summarizes the status quo on the adverse effects of the immunotherapeutic agents currently employed in cancer therapy. The topic covers an array of the affected systems (cardiovascular, dermatologic, endocrine, gastrointestinal, neurologic and pulmonary systems) and describes the known adverse effects caused by use of the specific agents. The reviewer finds this paper intriguing in that it is written for those who work in the clinic. It may help physicians to treat cancer patients properly with the immunotherapeutic agents and when they encounter the problems pertinent to the agents, they could find out the remedy. However, the reviewer has several concerns as follows: Major concerns; 1. Some basic insights into the mode of adverse effects are not properly explained. ex. 1. Some investigators have hypothesized that this overexpression may lead to excess monocytic activation, which infiltrate the thyroid gland, recognize self-antigens and induce subsequent cytotoxic damage to the normal cells[23]. It is not clear whether monocytic activation per se leads to cytotoxic damage to the normal cells or the damage is mediated by the self-antigen specific CD8 T cells which were activated by the monocytic cells. ex.2. but it is postulated that it may be due to autoreactive CD8+ t cell activation against pancreatic beta cells, which are now unable to bind to T cells and promote self-tolerance[27]. Readers cannot understand what the above sentence means. ex.3. Bronchoalveolar lavage may help immunosuppressed patients or in patients difficult to establish; however, a negative BAL does not exclude infection[52]. Readers cannot understand what the above sentence means. 2. It is highly desirable to use unified format to designate the therapeutic agents such as monoclonal antibody and antibody. A good example is “Ipilimumab, a CTLA-4 inhibitor”. It is not reader friendly to use only “Ipilimumab” as readers expect to have a brief description of the products to further their knowledge. 3. Related to 2, prepare a

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table summarizing the name of each therapeutic agent and brief description as above (ex. both Pembrolizum and Nivolumab are the humanized monoclonal antibody against PD1). 4. It is not acceptable that the authors did not discuss about CD19-expressing CAR-T cell therapy against B cell lymphoma and immune-related adverse events (irAEs). This is indispensable for the review. Minor concerns; 1. In A "which are normally utilized by healthy cells to promote self-tolerance and inhibit T-cell destruction{8}." It is not clear from this sentence whether T cells are destructed or destruction of tumor cells are inhibited. 2. In B "T-Cell transfer therapy creates tumor specific T-Cells that promote immune mediated destruction of cancers." This sentence is difficult to understand for readers outside the field. Rewrite so that a wide range of readers can understand. 3. In C "Monoclonal antibodies are engineered to be antigen specific, often tumor-specific, and mediate the destruction of tumor cells via direct tumor cell killing," The above sentence is quite confusing in that it can be interpreted that monoclonal antibodies per se kill tumor cells. Tumor cell killing is not direct and is rather caused by Antigen-dependent cellular cytotoxicity (ADCC). 4. There are some typographic errors and an error in abbreviation in the pulmonary system for "immune-related adverse events".

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PEER-REVIEW REPORT

Name of journal: World Journal of Clinical Oncology

Manuscript NO: 60532

Title: Systemic Adverse Effects and Toxicities Associated With Immunotherapy: A Review

Reviewer's code: 03001454
Position: Peer Reviewer
Academic degree: PhD

Professional title: Professor

Reviewer's Country/Territory: China

Author's Country/Territory: United States

Manuscript submission date: 2020-11-03

Reviewer chosen by: Jin-Lei Wang

Reviewer accepted review: 2020-12-31 03:48

Reviewer performed review: 2021-01-06 01:06

Review time: 5 Days and 21 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
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SPECIFIC COMMENTS TO AUTHORS

Immunotherapy becames a popular treatment against a wide variety of maligancies. The encouraging effectivity has been repeatedly repotrted from teams over the world. However, the negative sides have been largely ignored. The review article gave an extensive introduction about the immune related adverse effects (irAEs) to various organs/systems caused by immunotherapies. The article is helpful for clinicians and patients to better understand immunotherapies from both the positive and negative sides. the title "Discussion" after the section of Introduction is quite confused. The content is still the essential part of Introduction. The title is not necessary.

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RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: World Journal of Clinical Oncology

Manuscript NO: 60532

Title: Systemic Adverse Effects and Toxicities Associated With Immunotherapy: A Review

Reviewer's code: 01851506
Position: Peer Reviewer
Academic degree: PhD

Professional title: Professor

Reviewer's Country/Territory: Japan

Author's Country/Territory: United States

Manuscript submission date: 2020-11-03

Reviewer chosen by: Han Zhang (Part-Time Editor)

Reviewer accepted review: 2021-01-22 07:59

Reviewer performed review: 2021-01-23 01:33

Review time: 17 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
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The authors have revised the article according to the reviewer's recommendation. The quality of the article has improved and the problems pertinent to CAR-T cell therapy have been discussed. However, the reviewer still finds minor errors in the CART section. 1. Chimeric antigen receptor (CAR) T-cell therapy is a type of T-cell transfer therapy currently approved for the treatment several hematologic malignancies, including acute lymphoblastic leukemia and diffuse large B-cell lymphoma[53]. should be Chimeric antigen receptor (CAR) T-cell therapy is a type of T-cell transfer therapy currently approved for the treatment of several hematologic malignancies, including acute lymphoblastic leukemia and diffuse large B-cell lymphoma[53]. 2. Tocilizumab is not IL-6 inhibitor, it is an inhibitor of IL-6 receptor. 3. "They also recommend repeating the dose if there are not signs of clinical improvement over 24 to 48 h[56]." Should be "They also recommend repeating the dose if there are no signs of clinical improvement over 24 to 48 h[56]." 4. Symptoms normally being within the first 7 days following CAR T-cell infusion[59]. There is no verb.