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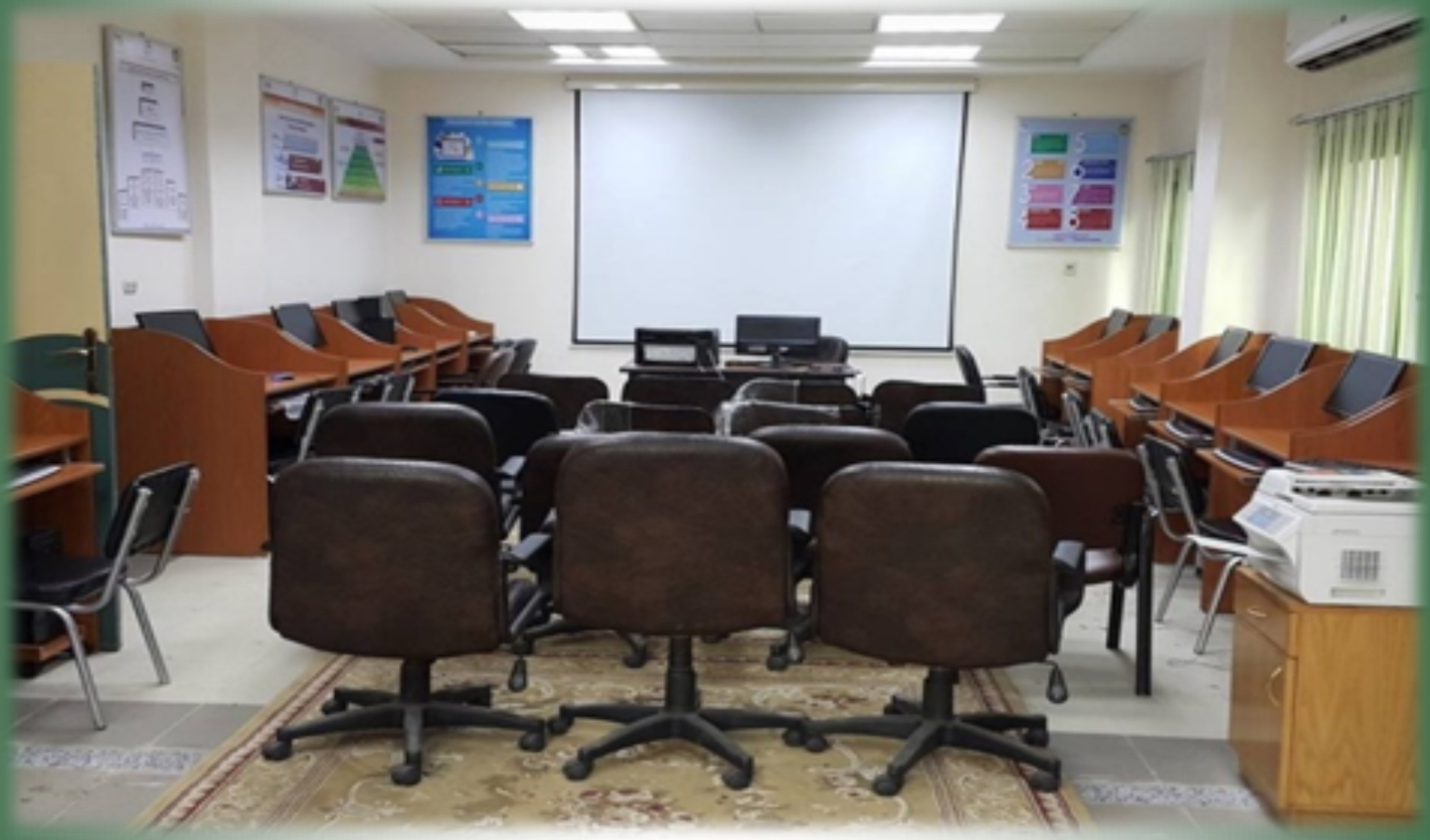

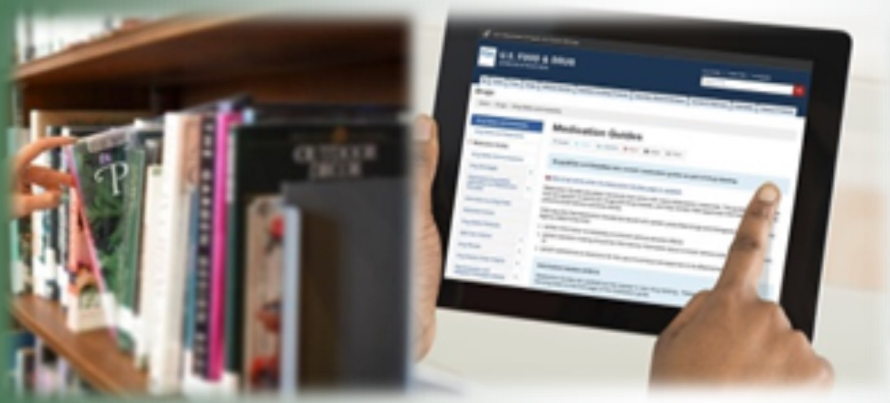

In this issue

By: Ph/Bassant Maher, M.Sc.

NOT all published clinical studies for the COVID-19 pandemic come into clinical useful decisions !!

For about one year, and till now, all the world is suffering from the novel pandemic coronavirus disease 2019 (COVID-19). Enormous number of hypothetical and clinical studies is published aiming at finding out possible prophylactic and therapeutic issues for controlling this aggressive disease. As we need emerging evidence, the publication processes for these issues come on board rapidly even in very high impacted and prestigious journals. Unfortunately, not all published data are well-designed and could be translated to clinical useful impact.

For example, a paper by **Joyner et al.** entitled "*Safety Update: COVID-19 Convalescent Plasma in 20,000 Hospitalized Patients*" was published in the Mayo Clinic Proceedings journal[1]. This study aimed at providing an update on key safety metrics after transfusion of convalescent plasma in 20,000 hospitalized COVID-19 patients and concluded that, transfusion of convalescent plasma is safe in those patients with supporting the notion that earlier administration of plasma within the clinical course of COVID-19 is more likely to reduce mortality.

Let's talk about the key elements of this paper:

- The impact factor of the Mayo Clinic Proceedings journal is 6.942 in 2019, which is high, and it is ranked one of the top 8% of the general and internal medicine.
- The authors come from high impacted medical institutions as U.S. Food and Drug Administration, Johns Hopkins Bloomberg School of Public Health, Mayo Clinic, College of Human Medicine - Michigan State University, and Cooper Medical School of Rowan University - Cooper University Health Care.

These issues made us feel that this paper is clinically important. While by coming on depth in the paper, let's discuss its limitations which were published as Letter To The Editor by **Youssef M.K. Farag2** *(ORCID ID: https://orcid.org/JMCP3152_0000-0003-1692-1851):*

- It seems that the reported cumulative incidence proportion of mortality is crude and was not adjusted for potential confounders, which makes it impossible for the authors to decisively attribute, or not, whatever they observe regarding convalescent plasma.

- This is a large case series with no comparison group; it is not appropriate to make any inferential statements. This includes the authors' strong statements on no increased risk of adverse cardiac or thrombotic/thromboembolic events or low mortality. So, the comparison group is warranted.
- Time since first symptom, hospitalization, intensive care unit admission, and mechanical ventilation to convalescent plasma transfusion should have been reported to take into account their potential impact on the timing of transfusion on mortality.
- The paper reported important insights on the significant variability in the temporal trends of key variables that may lead us to conclude that pooling the mortality proportion without stratifying by calendar month may not have been appropriate.
- The authors state that"[this study].support[s] the notion that earlier administration of plasma within the clinical course of COVID-19 is more likely to reduce mortality." No data are provided to directly or indirectly support this. No comparison group, no temporal data on the natural progression of the disease in relation to convalescent plasma transfusion, no statistical adjustment for potential confounders, and no adjusted subgroup or sensitivity analyses.
- Comparing these 20,000 patients to a group of controlled patients would significantly contribute to the body of evidence in this area, not only in terms of safety but also effectiveness to reduce mortality, or even better, a randomized controlled trial to assess efficacy to reduce mortality.

Although the authors replied to this letter and explained scientifically all these reported limitation, we as a Drug and Poison Information specialists recommend the following:

All health care professionals should learn designing, interpreting, peer-reviewing, and criticism the clinical research studies that will enable them to pick out the suitable clinical decisions used in their

References:

⇒ ***Joyner MJ, Bruno KA, Klassen SA, et al. Safety Update: COVID-19 Convalescent Plasma in 20,000 Hospitalized Patients. Mayo Clin Proc. 2020;95(9):1888-1897. doi:10.1016/j.mayocp.2020.06.028.***

⇒ ***Farag Y. Limitations of Safety Update on Convalescent Plasma Transfusion in COVID-19 Patients. Mayo Clin Proc. 2020;95(12): 2801-2802. doi: 10.1016/j.mayocp.2020.09.033.***

By: Bassant M. Mahboub, M.Sc

Research area

An area for new research ideas/points in different fields of pharmacy practice.

Nanotechnology for management of cancer stem-like cells (CSCs)

Tumor heterogeneity remains a major challenge in cancer therapy owing to the different susceptibility of cells to chemotherapy within a solid tumor. Cancer stem-like cells (CSCs), also referred to as **'tumor-initiating cells'**, have been considered to be one of the decisive factors accounting for intr-atumour heterogeneity, which show self-renewal, high tumourigenicity, invasiveness and resistance to traditional chemo - and radiotherapy. They are also shown to be much higher in the poorly differentiated tumors associated with high-grade malignancy and poor prognosis than that in the well-differentiated counterparts. Considerable efforts have been made to develop promising anti-CSC strategies, including blocking the surface biomarkers and inhibiting the self-renewal signaling pathways.

Differentiation therapy is a clinical approach to coaxing malignant cells to differentiate into more mature phenotypes with a less stem-like undifferentiated state using differentiation-inducing agents that are often less toxic than conventional chemotherapeutic drugs. Mounting evidence substantiates that differentiation reduces the proportion of CSCs in various solid tumors. Its hallmark achievement is the application of all-trans retinoic acid (ATRA) and arsenic, inducing complete remission in patients with acute promyelocytic leukaemia. However, differentiation therapy for solid tumors suffers from non-shrinking tumor size and residual of massive bulk tumor cells. Importantly, CSCs can arise de-novo from the bulk tumor cells called ***de-differentiation***. In contrast, traditional mono-chemotherapy using cytotoxic drugs such as camptothecin ***(CPT),*** doxorubicin and paclitaxel not only cannot kill the highly resistant and mitotically quiescent CSCs efficiently, but also increase their 'stemness'-related properties.

Accordingly, a combination of differentiation therapy and chemotherapy to concurrently eliminate bulk tumor cells and CSCs has been recognized as a potent treatment tactic to combat the CSC-rooted heterogeneity. To this end, a refined strategy for the co-delivery of differentiation-inducing and chemotherapeutic agents remains elusive to achieve an optimal combinational efficacy in consideration of their distinct anticancer mechanisms.

All-trans-retinoic acid ***(ATRA)*** and ***CPT*** are selected as the model differentiation-inducing and cytotoxic drugs, respectively. To unify the differential pharmacokinetic and bio-distribution profiles, **ATRA** and **CPT** are co-loaded into one nano-carrier, which can maintain a fixed synergistic drug ratio in contrast to their cocktail physical mixture that suffers from a constantly changing ratio. In order to maximize the synergistic efficacy in eliminating CSCs, ATRA is required to be released from the nano-carrier first to induce CSCs to differentiate into their descendant non-CSCs with reduced stemness and chemo-resistance, which increases the sensitivity of CSCs to the subsequently released CPT and prevents CPT-stressed up-regulation of stemness. In this regard, ATRA and CPT can be formulated to be physically encapsulated and chemically conjugated into nanoparticles, respectively, to obtain sequential drug release. A polymer–drug conjugate, namely, nitro-imidazole-modified hyaluronic acid–oxalate–CPT conjugate ***(n-HA-oxa-CPT),*** is synthesized, which can assemble into nanoparticles and physically encapsulate ATRA to acquire ATRA/CPT-NPs.

ATRA/CPT-NPs can adaptively differentiate the release of two drugs during the differentiation of CSCs. Hypoxia has been identified as a predominant feature of the tumor microenvironment, particularly the CSC niche. After uptake by CSCs, ATRA/CPT-NPs rapidly release ATRA by a hypoxia-triggered structural change from the hydrophobic nitro-imidazole group to the hydrophilic amino-imidazole group .The released ATRA acts on the retinoic acid receptor and therefore induces CSC differentiation. CPT conjugated via a reactive oxygen species (ROS)-labile oxalate linkage is highly stable and minimally leaks from ATRA/CPT-NPs in undifferentiated CSCs with a low ROS level due to the increased expression of free radical scavengers, which averts both CPT efflux by CSCs and CPT-induced increase in CSC stemness. When the CSCs differentiate, the intracellular ROS level elevates with the generation of mitochondrial superoxide due to the increased mitochondrial biogenesis, which is positively correlated with the degree of differentiation. The rising ROS level leads to the release of CPT as the original drug molecule via oxalate linker degradation and enhanced cytotoxicity towards the differentiated descendent cells with decreased stemness and resistance. The study shows that ATRA/CPT-NPs can effectively inhibit the growth, relapse and metastasis of the CSC-enriched heterogeneous breast tumors in the mouse models. These findings provide a promising perspective for exploring the convergent nano-therapeutic approach to overcome the CSC-associated chemotherapeutic resistance.

References:

Shiyang Shen , Xiao Xu , Shiqi Lin, et al. A nanotherapeutic strategy to overcome chemotherapeutic resistance of cancer stem-like cells. Nat Nanotechnol, 2021 Jan;16(1):104-113. x̲h̲Ẑ 10.1038/s41565-020-00793-0

By: Marwa EL-Sayed, PGCPD.

About Us

Vision

Improving healthcare services within the society through provision of evidence-based, unbiased, patient oriented drug information services & adverse drug reporting system.

Activities

- Answering drug information requests.
- Scientific publishing & periodical drug bulletin.
- Pharmacivigilance activities.
- Continuous education activities.
- Research studies.

Online databases

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- Martindale: The Complete Drug Reference.
- Medical Dictionary for Regulatory Activities (MedDRA) databases.
- Drug Facts & Comparisons.

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⇒ **Facebook Page**
Drug Information Center-Faculty of Pharmacy-Tanta University.

⇒ **Landline:**
040-3331577-3336007(7-241)

⇒ **Hotline:**
090071020

⇒ **Email:**
Tanta_DPIC@pharm.tanta.edu.eg.