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Editorial

Immunotherapy in Medicine

The recent announcement of the 2018 Nobel Prize in Physiology or Medicine to James P. Allison and Tasuku Honjo for their discovery of cancer therapy by inhibition of negative immune regulation has focused attention on the importance of immunotherapy in the treatment of cancer and other medical illnesses. Immunotherapy is the treatment for disease by either stimulating or suppressing the immune system. Immunotherapies designed to elicit or amplify an immune response are known as activation immunotherapies, while those that suppress the immune response are classified as suppression immunotherapies.

William B. Coley first attempted to harness the immune system for treating cancer in 1891. He observed that some cancer patients went into remission after developing erysipelas. Assuming that their immune systems had become stimulated by the infection, he began injecting mixtures of live and inactivated Streptococcus Pyogenes and Serratia Marcescens into the tumors of cancer patients. He observed complete remission in some cancers including sarcoma, lymphoma, and testicular carcinoma. However, since there was no understandable mechanism for these responses and the thought of infecting patients with pathogenic bacteria was unacceptable, oncologists researched other treatments.

Thereafter, with the lack of complete remission with chemotherapy and radiotherapy in many cancers, oncologists began to consider the option of attenuated bacilli. In 1976, a trial was conducted to test the use of the tuberculosis vaccine Bacille Calmette-Guérin (BCG) as a means of preventing the recurrence of non-muscle invasive bladder cancer. BCG therapy was very effective and continues to be used today.

In the 1970s, Milstein and Köhler pioneered the production of monoclonal antibodies using hybridomas, antibody-secreting cell lines formed by the fusion of lymphocytes with myeloma cell lines. The work of Allison and Honjo is an extension of these early studies in immune stimulation. While the most common applications of immunotherapy are in the treatment of various types of cancers, there is evidence suggesting its efficacy in the treatment of inflammatory illnesses such as Crohn's Disease and Rheumatoid arthritis. It is also used in the treatment of infertility, particularly for the prevention of multiple miscarriages.

Although immunotherapy has been around for over a hundred years, its full potential is just beginning to unravel. Harnessing the body's own immune system to treat cancer and other medical illnesses minimizes the use of pharmacologic agents which have toxic and unpleasant effects on healthy cells. We can expect more miracles to emerge from this exciting field of research.

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Director, Medical Research.

Research Events

Dr. H. B Chandalia conducted a workshop on Research Methodology on 4th August 2018. Topics included were as follows:

- Conceiving and developing research concepts
- DNB thesis requirements
- Study design and protocol
- Statistical methods in biomedical research
- Ethical issues
- Effective reporting of research data
- Publishing research papers

Abstracts

Antioxidants as precision weapons in war against cancer chemotherapy induced toxicity - Exploring the armoury of obscurity
Singh K, Bhori M, Kasu YA, Bhat G, Marar T
Saudi Pharmaceutical Journal 2018; 26:177-190.

Cancer is the leading cause of mortality worldwide, accounting for almost 13% of deaths in the world. Among the conventional cancer treatments, chemotherapy is most frequently carried out to treat malignant cancer rather than localised lesions which is amenable to surgery and radiotherapy. However, anticancer drugs are associated with a plethora of side effects. Each drug, within every class, has its own set of adverse reactions which may cause patient incompliance and deterioration of the quality of life. One of the major causes of adverse reactions, especially for drugs targeting DNA, is the excessive production of reactive oxygen species (ROS) and subsequent build-up of oxidative stress. To curb these undesired side effects, several dietary supplements have been tested, amongst which antioxidants have gained increasing popularity as adjuvant in chemotherapy. However, many oncologists discourage the use of antioxidant rich food supplements because these may interfere with the modalities which kill cancer by generating free radicals. In the present review, all studies reporting concomitant use of several antioxidants with chemotherapy are indiscriminately included and discussed impartially. The effect of supplementation of thirteen different antioxidants and their analogues as a single agent or in combination with chemotherapy has been compiled in this article. The present review encompasses a total of 174 peer-reviewed original articles from 1967 till date comprising 93 clinical trials with a cumulative number of 18,208 patients, 56 animal studies and 35 *in vitro* studies. Our comprehensive data suggests that antioxidant has superior potential of ameliorating chemotherapeutic induced toxicity. Antioxidant supplementation during chemotherapy also promises higher therapeutic efficiency and increased survival times in patients.

Unproven therapies for Diabetes and their implications
Kesavadev J, Saboo B, Sadikot S, Das AK, Joshi S, Chawla R, Thacker H, Shankar A
Advances in Therapy 2017; 34:60-77.

Diabetes is a chronic disease and is one of the leading causes of morbidity and mortality worldwide. Being an ancient disease, many individuals follow complementary and alternative medicinal (CAM) therapies for either the cure or prevention of the disease. The popularity of these practices among the general public is in no way a testimony to their safety and efficacy. Due to the possibility of undesirable interactions with conventional medicines, it is imperative that patients are asked about CAM use during patient assessment. Patient- and physician-targeted awareness programs on various aspects of CAM use must be initiated to create a better understanding of evidence-based use of these practices. In addition, there should be guidelines in place based on clinical trial outcomes, and stricter regulations need to be enforced on CAM practices to ensure their safety and effectiveness.

Prophylactic propranolol for prevention of ROP and visual outcome at 1 year (PreROP trial)
Sanghvi KP, Kabra NS, Padhi P, Singh U, Dash SK, Avasthi BS
Archives of Disease in Childhood - Fetal and Neonatal 2017; 102:F389-F394.

OBJECTIVE: To evaluate the role of prophylactic propranolol in the prevention of retinopathy of prematurity (ROP) in infants ≤32 weeks of gestational age and their visual outcome at 1 year of corrected gestational age.

DESIGN: Randomised double blind placebo controlled trial, parallel group enrolment with allocation ratio of 1:1.

SETTINGS: Two level III neonatal intensive care units.

PARTICIPANTS: 109 preterm neonates of ≤32 weeks of gestation with postnatal age ≤8 days old.

RESULTS: Prophylactic propranolol in the prescribed dose of 1 mg/kg/day showed a decreasing trend in the incidence of ROP (56.8% vs 68.6%; p=0.39), need for laser therapy (21.56% vs 31.37%; p=0.37), treatment with anti-VEGF (3.92% vs 15.68%; p=0.09) or visual outcomes at 1 year in the study and control groups, respectively, though these reductions were not statistically significant. Decreasing trends favouring propranolol in all other ROP-related outcomes were also noted in the study group.

CONCLUSIONS: Prophylactic propranolol in the prescribed dose of 1 mg/kg/day showed a decreasing trend in all outcomes of ROP though statistically not significant.

Classification of Trigeminal Autonomic Cephalalgia: What has changed in International Classification of Headache Disorders-3 Beta?

Ravishankar K

Annals of Indian Academy of Neurology 2018; 21:S45-S50.

The term "Trigeminal Autonomic Cephalalgia (TAC)" was first coined by Goadsby and Lipton[1] to include a group of relatively rare primary headache disorders characterized by moderate to severe, short-lived head pain in the trigeminal distribution with unilateral cranial parasympathetic autonomic features, such as lacrimation, rhinorrhea, conjunctival injection, eyelid edema, and ptosis. In the current International Classification of Headache Disorders (ICHD-3 beta),[2] the TAC group includes cluster headache (CH), paroxysmal hemicrania (PH), short-lasting unilateral neuralgiform headache attacks (SUNHAs) and their 2 subforms - SUNHAs with conjunctival injection and tearing (SUNCT), SUNHAs with cranial autonomic symptoms (SUNA). Hemicrania Continua (HC) is also now included in the TAC group. Although the entities included under TACs seem broadly similar, they differ in attack duration, frequency and their response to different treatments. At one end of the spectrum lies CH, the prototypic TAC where the duration of attacks is the longest and at the other end is the SUNCT syndrome where the duration is shortest. There is some overlap across the entities; they are not difficult to recognize and subclassify. The umbrella term "TAC" for the short-lasting headaches with autonomic features was for the first time introduced in The ICHD, 2nd edition (ICHD-2) published in 2004.[3] The beta version of the 3rd edition of The ICHD[2] was published in 2013. Headache classification being an evolving process, there have been some changes within the TAC group between ICHD-2 and ICHD-3 beta.[45] Diagnostic criteria have been revised to reflect pathophysiological and clinical observations. Neuroimaging has provided insights into the pathophysiology of TACs. Functional neuroimaging has helped to elucidate key structures activated during attacks of TACs. Correct diagnosis remains the key to correct management of the TACs because treatment options vary. The aim of this article will be to highlight the changes in ICHD-3 beta to this group and to emphasize the clinical implications of these changes. Description of individual entities included under TACs are included elsewhere and will therefore not be detailed here.

The emergence of Kawasaki disease in India and China

Jiao F, Jindal AK, Pandiarajan V, Khubchandani R, Kamath N, Sabui T, Mondal R, Pal P, Singh S

Global Cardiology Science & Practice 2017(3):e201721.

Kawasaki disease (KD) is recognized as a leading cause of acquired heart disease in children in developed countries. Although global in distribution, Japan records the highest incidence of KD in the world. Epidemiological reports from the two most populous countries in the world, namely China and India, indicate that KD is now being increasingly recognized. Whether this increased reporting is due to increased ascertainment, or is due to a true increase in incidence, remains a matter of conjecture. The diagnosis and management of KD in developing countries is a challenging proposition. In this review we highlight some of the difficulties faced by physicians in managing children with KD in resource-constrained settings.

Comparison of CD9 & CD146 markers in endometrial stromal cells of fertile & infertile females

Chaudhari-Kank MS, Zaveri K, Antia V, Hinduja I

Indian Journal of Medical Research 2018; 147:552-559.

BACKGROUND & OBJECTIVES: CD9 and CD146 are important adhesion molecules that play a role in the implantation of an embryo. This study was undertaken to correlate the expression of these markers in fertile and infertile women's endometrial stromal cells.

METHODS: Human endometrial stromal cell culture from endometrial biopsies of fertile (n=50) and infertile females (n=50) was performed and primary cell lines were established. Expression of CD9 and CD146 was studied for all the 100 cell lines with the help of flow cytometry. Gene expression of CD9 and CD146 was performed by real-time polymerase chain reaction.

RESULTS: There was a significant difference in endometrial stromal cells of fertile and infertile females. Flow cytometric results revealed significantly lower expression of CD9 (P=0.0126) and CD146 (P=0.0006) in the infertile endometrial stromal cells as compared to fertile endometrial stromal cells. These results were comparable with real-time data.

INTERPRETATION & CONCLUSIONS: This study showed that endometrial stromal cells from infertile females had lower expression of adhesion molecules, CD9 and CD146. Our findings suggest that CD9 and CD146 may have a role in infertility. Infertile female's endometrial stromal cells have decreased expression of CD9 and CD146 which can be the cause of infertility related to implantation failure.

Evidence-based clinical practice points for the management of venous ulcers.

Jindal R, Dekiwadia DB, Krishna PR, Khanna AK, Patel MD, Padaria S, Varghese R

Indian Journal of Surgery 2018; 80:171-182.

Venous ulcer is an extremely common aetiology of lower extremity ulceration, which affects approximately 1% population in most of the countries, and the incidence rate increases with age and female gender. Proper assessment and diagnosis of both the patient and ulcer are inevitable in order to differentiate venous ulcers from other lower extremity ulceration and to frame an adequate and individualised management plan. Venous ulcers generally persist for weeks to many years and are typically recurrent in nature. This consensus aims to present an evidence-based management approach for the patients with venous ulcers. Various management options for venous ulcers include compression therapy, minimally invasive procedures like sclerotherapy and ablation techniques, surgical procedures, debridement and medical management with micronised purified flavonoid fraction (MPFF). Compression therapy is the mainstay treatment for venous ulcer. However, in failure cases, surgery can be preferred. Medical management with MPFF as an adjuvant therapy to standard treatment has been reported to be effective and safe in patients with venous ulcer.

Nobel Prize in Physiology or Medicine 2018

The 2018 Nobel Prize in Physiology or Medicine was awarded to ***James P. Allison***, from the University of Texas MD Anderson Cancer Center in Houston, and ***Tasuku Honjo***, from Kyoto University in Japan, for their discovery of cancer therapy by inhibition of negative immune regulation.

Allison and Honjo's research led to the development of a novel therapy: monoclonal antibodies that block the regulatory pathways controlled by CTLA-4 and PD-1. Instead of targeting the tumor cells themselves, our own immune cells are given a boost by 'releases the brakes on the immune cells'. These drugs, called Immune Checkpoint Inhibitors. These new antibody-drugs have led to dramatic tumor regressions.

Allison, an immunologist, studied a protein receptor called CTLA-4 on T-cells. CTLA-4 acts like a brake, keeping the immune system in check. He realized that by blocking this brake the immune cells could be unleashed on tumor cells. Based on this principle, in 2011 a drug based on CTLA-4, Ipilimumab, was approved for treating Melanoma. More than 20 percent of people using the drug have complete remission from the disease.

Honjo, also an immunologist, discovered a second receptor on T tells called PD-1 that also acted as a brake to the immune system, but with a different mechanism of action. Blocking the PD-1 receptor lead to boosting the immune system against cancer cells. Two drugs based on PD-1 inhibition, Nivolumab and Pembrolizumab, have been approved for treating Melanoma and Lung Cancer.

Checkpoint inhibitors have proved to be successful treatments for a variety of advanced cancers such as: metastatic melanoma, lung cancer, kidney cancer, bladder cancer, head and neck cancers, and other tumors. Combinations of the two types can be even more effective.

The work of Allison and Honjo has revolutionized our understanding of the immune system and has created a fundamental change in the practice of oncology. Their work will alter the treatment of several malignancies in the foreseeable future and affect innumerable lives.

Editorial Board