

Hot Articles

“April|2017”

Health Science



Title: [A Simulation Study to Compare the Treatment Effect of Tamoxifen by CYP2D6 Genotypes and Third-Generation Aromatase Inhibitors](#)

Author: Gwan Cheol Park, Jin-A Jung, Kyun-Seop Bae and Hyeong-Seok Lim

Journal: The Journal of Clinical Pharmacology

Volume: Version of Record online: 3 APR 2017

Doi: DOI: 10.1002/jcph.896

Abstract

Some prospective, randomized clinical trials, including ATAC and BIG 1–98, demonstrated superior treatment effect of third-generation aromatase inhibitors (AIs) versus tamoxifen in postoperative therapy for patients with breast cancer. In retrospective genotyping analyses of the 2 studies using tumor samples, no difference in the treatment effect of tamoxifen was observed by CYP2D6 genotypes. However, those analyses did not consider loss of heterozygosity that could have occurred when genotyping using tumor tissue. The present simulation study aimed to comparatively evaluate the treatment effect of tamoxifen versus AIs of anastrozole and letrozole by CYP2D6 genotypes. A meta-analysis was conducted to estimate disease-free survival (DFS) hazard ratios of CYP2D6 genotypes representing extensive metabolizers (EMs), HRW/W,TAM, versus intermediate metabolizers (IMs)/poor metabolizers (PMs), HRV/W,TAM, using previous study results in which genotypes were determined using blood samples. Based on known allele frequencies, the CYP2D6 genotype distribution of participants in ATAC and BIG 1–98 trials were simulated. Subsequently, DFS HRs of AIs versus tamoxifen by CYP2D6 genotypes (HRAI/TAM,W for EMs, HRAI/TAM,V for IMs/PMs) were estimated via regression analyses using NONMEM, based on the simulated genotype distributions, HRV/W,TAM, and HRs, of AIs versus tamoxifen (HRAI/TAM) reported in the ATAC and BIG 1–98 trials. Median HRAI/TAM,V (95% prediction interval [PI]) was 0.43 (0.23–0.79) and 0.40 (0.22–0.73) for the ATAC and BIG 1–98 trials, respectively. However, the corresponding HRAI/TAM,W values were 0.97 (0.84–1.11) and 0.91 (0.77–1.08), respectively. These results suggest that in patients with the CYP2D6 genotype representing EMs, the treatment effect of tamoxifen is comparable to that of AIs.

Database

Wiley Online Library

Title: [Critical appraisal of clinical practice guidelines for adult cancer patients with febrile neutropenia](#)

Author: Ziad G. Nasr, Safae Abu Yousef, Farah Jibril and Kyle J. Wilby

Journal: International Journal of Pharmacy Practice

Volume: Version of Record online: 27 MAR 2017

Doi: DOI: 10.1111/ijpp.12357

Abstract

Objectives

To critically appraise published international clinical practice guidelines (CPGs) for management of febrile neutropenia in adult patients with cancer and to determine opportunities for improved development and reporting.

Methods

A literature search identified CPGs for adult cancer patients with febrile neutropenia. Four independent assessors evaluated each included CPG according to the Appraisal of Guidelines for Research and Evaluation II instrument. Standardized scores were calculated for each guideline and pooled collectively. Reliability of assessment was determined using a two-way random model intraclass correlation coefficients.

Key findings

Eight CPGs were independently evaluated by four assessors. Collectively, the highest scoring domain was editorial independence (83.3), followed by clarity of presentation (55.4), scope and purpose (53.4), stakeholder involvement (53.1), rigour of development (52.7) and applicability (47.8). Overall assessments ranged from 28.6 to 96.4 of 100 possible points. Three (37.5%) guidelines were recommended for use without alterations, two (25%) guidelines were recommended with alterations, and three (37.5%) guidelines were not recommended for implementation into practice. Reliability varied between guidelines with intraclass correlation coefficients ranging from 0.41 to 0.82.

Conclusions

Clinical practice guidelines for febrile neutropenia in adult patients with cancer were moderately rated with a 37.5% of guidelines being recommended for use in practice. Guideline developers should focus on improving CPG applicability and rigour in the development and reporting processes. Critical appraisal of guidelines should become a standard practice prior to implementation into clinical settings.

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Wiley Online Library

Title: [The antiproliferative and apoptotic effects of apigenin on glioblastoma cells](#)

Author: Trevor A. Stump, Brittany N. Santee, Lauren P. Williams, Rachel A. Kunze, Chelsae E. Heinze, Eric D. Huseman, Rebecca J. Gryka, Denise S. Simpson and Samson Amos

Journal: Journal of Pharmacy and Pharmacology

Volume: Version of Record online: 28 MAR 2017

Doi: DOI: 10.1111/jphp.12718

Abstract

Objectives

Glioblastoma (GBM) is highly proliferative, infiltrative, malignant and the most deadly form of brain tumour. The epidermal growth factor receptor (EGFR) is overexpressed, amplified and mutated in GBM and has been shown to play key and important roles in the proliferation, growth and survival of this tumour. The goal of our study was to investigate the antiproliferative, apoptotic and molecular effects of apigenin in GBM.

Methods

Proliferation and viability tests were carried out using the trypan blue exclusion, MTT and lactate dehydrogenase (LDH) assays. Flow cytometry was used to examine the effects of apigenin on the cell cycle check-points. In addition, we determined the effects of apigenin on EGFR-mediated signalling pathways by Western blot analyses.

Key findings

Our results showed that apigenin reduced cell viability and proliferation in a dose- and time-dependent manner while increasing cytotoxicity in GBM cells. Treatment with apigenin-induced is poly ADP-ribose polymerase (PARP) cleavage and caused cell cycle arrest at the G2M checkpoint. Furthermore, our data revealed that apigenin inhibited EGFR-mediated phosphorylation of mitogen-activated protein kinase (MAPK), AKT and mammalian target of rapamycin (mTOR) signalling pathways and attenuated the expression of Bcl-xL.

Conclusion

Our results demonstrated that apigenin has potent inhibitory effects on pathways involved in GBM proliferation and survival and could potentially be used as a therapeutic agent for GBM.

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Wiley Online Library

Title: [Quantification of Exosomes](#)
Author: Erik H. Koritzinsky, Jonathan M. Street, Robert A. Star and Peter S.T. Yuen
Journal: Journal of Cellular Physiology
Volume: 232 **Issue:** 7 **Page:** 1587–1590 (July 2017)
Doi: 10.1002/jcp.25387

Abstract

Exosomes are released by cells as self-contained vesicles with an intact lipid bilayer that encapsulates a small portion of the parent cell. Exosomes have been studied widely as information-rich sources of potential biomarkers that can reveal cellular physiology. We suggest that quantification is essential to understand basic biological relationships between exosomes and their parent cells and hence the underlying interpretation of exosome signals. The number of methods for quantifying exosomes has expanded as interest in exosomes has increased. However, a consensus on proper quantification has not developed, making each study difficult to compare to another. Overcoming this ad hoc approach will require widely available standards that have been adequately characterized, and multiple comparative studies across platforms. We outline the current status of these technical approaches and our view of how they can become more coherent.

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Wiley Online Library

Title: [Stem Cells Applications in Bone and Tooth Repair and Regeneration: New Insights, Tools and Hopes](#)

Author: Eiman Abdel Meguid, Yuehai Ke, Junfeng Ji and Ahmed HK El-Hashash

Journal: Journal of Cellular Physiology

Volume: Accepted manuscript online: 30 MAR 2017

Doi: 10.1002/jcp.25940

Abstract

The exploration of stem and progenitor cells holds promise for advancing our understanding of the biology of tissue repair and regeneration mechanisms after injury. This will also help in the future use of stem cell therapy for the development of regenerative medicine approaches for the treatment of different tissue-specie defects or disorders such as bone, cartilages and tooth defects or disorders. Bone is a specialized connective tissue, with mineralized extracellular components that provide bones with both strength and rigidity, and thus enable bones to function in body mechanical supports and necessary locomotion process. New insights have been added to the use of different types of stem cells in bone and tooth defects over the last few years. In this concise review, we briefly describe bone structure as well as summarize recent research progress and accumulated information regarding the osteogenic differentiation of stem cells, as well as stem cell contributions to bone repair/regeneration, bone defects or disorders and both restoration and regeneration of bones and cartilages. We also discuss advances in the osteogenic differentiation and bone regeneration of dental and periodontal stem cells as well as in stem cell contributions to dentine regeneration and tooth engineering. This article is protected by copyright. All rights reserved

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Title: [Supporting successful inclusive practices for learners with disabilities in high schools: a multisite, mixed method collective case study](#)

Author: Donald Maciver, Cathleen Hunter, Amanda Adamson, Zoe Grayson, Kirsty Forsyth & Iona McLeod

Journal: Disability and Rehabilitation

Volume: Published online: 04 Apr 2017

Doi: 10.1080/09638288.2017.1306586

Abstract

Purpose: The increase in the number of individuals with disabilities in general education has led to an increased interest in how to best provide support. Despite an emphasis on inclusion and participation in policy and practice, defining and describing the support provided for these learners is still an important task.

Method: This multisite, mixed method collective case study reports on 125 education and other staff from seven schools who took part in interviews and focus groups to reflect on a range of topics related to learners with disabilities in high schools. We focused on what the participants did, what they considered to be successful and what their “best” practices were.

Results: Descriptions of practices were rich, nuanced and complex. The analysis identified over 200 “strategies” which were synthesized into two meta-themes and eight subthemes. We discuss the results in the context of an ecological perspective, and the importance of focusing on the full range of influences and outcomes for young people in designing supports.

Conclusions: We have drawn on evidence from this study as a basis for professional development activities and identified that focusing on the environment and the role of practitioners has a potential to improve the inclusion outcomes for older learners with disabilities.

Database

Taylor & Francis Online Journal

Title: [An exploration of physiotherapists' experiences of robotic therapy in upper limb rehabilitation within a stroke rehabilitation centre](#)

Author: Andrew Stephenson & John Stephens

Journal: Disability and Rehabilitation: Assistive Technology

Volume: Published online: 01 Apr 2017

Doi: 10.1080/17483107.2017.1306593

Abstract

Purpose: Strokes are the world's leading cause of adult disability, with movement impairment being more common in the upper limb (UL). Robotic therapy (RT) is identified as an effective adjunct to promote movement but with limited effect on functional capabilities. There is currently limited research in user experience of RT, specifically that of physiotherapists. This study sought to explore physiotherapists' experience of using RT in rehabilitation of the UL, within a stroke rehabilitation centre in the north of England.

Method: Physiotherapists (n = 6) shared their experiences of working with the InMotion2 robot through semi-structured interviews. Thematic analysis was employed to interpret data, identify emergent themes and interdependent relationships between them.

Findings: Five interdependent themes were identified focused around individualized care, influenced by evidence for practice, human relationships, skill mix, and resources and resource management. All physiotherapists valued the use of RT as an adjunct to conventional therapy, although barriers to successful implementation seemed to dominate the views of some.

Conclusions: RT was perceived positively by physiotherapists, regarded as an adjunct to conventional therapy. A framework to summarize the relationships of participants' views and experiences is proposed in an attempt to understand the influences on the clinical use of RT.

Database

Taylor & Francis Online Journal

Title: [Pembrolizumab use for the treatment of advanced melanoma](#)
Author: Pol Specenier
Journal: Expert Opinion on Biological Therapy
Volume: Published online: 03 Apr 2017
Doi: 10.1080/14712598.2017.1309388

Abstract

Introduction: Until recently, overall long term survival in patients with stage IV melanoma was lower than 10%. However, the treatment of melanoma has evolved rapidly over the last few years, with the advent of inhibitors of BRAF and MEK and of immunotherapeutic agents including ipilimumab, nivolumab, and pembrolizumab.

Areas covered: This is a comprehensive review of the literature on the role of pembrolizumab in melanoma. Pembrolizumab is a Programmed Death Receptor 1 (PD-1) directed monoclonal antibody which is approved by FDA and EMA for the treatment of patients with metastatic melanoma.

Expert opinion: Phase II and III trials demonstrated that pembrolizumab is superior to ipilimumab in previously untreated patients and to chemotherapy in ipilimumab pre-treated patients. Unfortunately, prospectively validated predictive markers are lacking. Immune-related adverse events are particularly interesting and should be managed per the published guidelines. There are still many issues that remain unresolved including: when to stop treatment, biomarkers for choosing a single agent or combination therapy, the optimal schedule of ipilimumab in combination with anti-PD1 monoclonal antibodies, optimal management of adverse events, the role of immunotherapy in specific populations, the optimal sequence of immunotherapy and the BRAF/MEK inhibitor combination in patients.

Database

Taylor & Francis Online Journal

Title: [The value of microparticles in detecting acute rejection episodes after liver transplantation](#)

Mehmet Haluk Morgul, Katrin Splith, Christoph Leonhardt, Nathanael Raschzok, Anja Reutzel-Selke, Rosa Bianca

Author: Schmuck, Andreas Andreou, Georgi Atanasov, Christian Benzing, Felix Krenzien, Hans-Michael Hau, Philipp Felgendreff, Sergej Klunk, Johann Pratschke, Igor Maximillian Sauer & Moritz Schmelzle

Journal: Biomarkers

Volume: Published online: 03 Apr 2017

Doi: 10.1080/1354750X.2017.1306754

Abstract

Context: Non-invasive markers for diagnosis of acute rejection (AR) following liver transplantation have not been developed, yet.

Objective: We analyzed the correlation of plasma microparticle levels (MP) with AR.

Materials and Methods: MP (CD4, CD8, CD25, CD31, MHC) of 11 AR patients and 11 controls were analyzed within the first week after transplantation.

Results: CD4, CD8 and CD31 positive MP were higher in the AR, whereas overall MP count, CD25 and MHC1 positive MP proportions did not differ between both groups.

Discussion and Conclusion: MP dynamics within the first period of transplantation could help to clarify on-going mechanisms of immunomodulation.

Database

Taylor & Francis Online Journal

Title: [Corrosive-Induced Carcinoma of Esophagus: Esophagographic and CT Findings](#)
Author: Seung Yeon Noh, et al.
Journal: American Journal of Roentgenology
Volume: Mar 23, 2017 (Ahead of Print)
Doi: 10.2214/AJR.16.17138

Abstract

OBJECTIVE. The purpose of this study was to evaluate the esophagographic and CT findings of corrosive esophageal cancer.

MATERIALS AND METHODS. The records of all patients who presented with corrosive esophageal strictures at one institution between June 1989 and April 2015 were retrospectively identified. The search yielded the records of 15 patients with histopathologically proven esophageal cancer. Esophagograms (13 patients) and chest CT images (14 patients) were interpreted independently by two reviewers. Esophagographic findings included the location of tumor, morphologic type, presence and length of mucosal irregularity, presence of asymmetric involvement, and presence of rigidity. CT findings included presence and type of esophageal wall thickening, pattern of enhancement, presence of periesophageal infiltration, and presence of hilar or mediastinal lymphadenopathy.

RESULTS. Esophagography showed that the tumor was involved with the stenotic portion in 10 of the 13 patients (76.9%). The most common morphologic feature was a polypoid mass, in 10 patients. In 12 patients (92.3%), mucosal irregularities were observed; the mean affected length was 4.92 cm. Asymmetric involvement and rigidity were observed in nine patients (69.2%). On CT scans, eccentric wall thickening was observed in 10 of the 14 patients (71.4%), homogeneous enhancement in nine (64.2%), and periesophageal infiltration in 11 (78.5%).

CONCLUSION. Esophagography commonly shows corrosive esophageal cancer as a polypoid mass with long-segment mucosal irregularities at the stenotic portion, asymmetric involvement, and rigidity. CT shows eccentric esophageal wall thickening with homogeneous enhancement and periesophageal infiltration, which are suggestive of the development of malignancy in patients with corrosive esophageal strictures.

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