ISSN 2218-4333 (online)

World Journal of *Clinical Oncology*

World J Clin Oncol 2012 January 10; 3(1): 1-14

Baishideng Publishing Group
www.wjgnet.com

WJCO World Journal of Clinical Oncology

A peer-reviewed, online, open-access journal of oncology

Editorial Board

2010-2014

The *World Journal of Clinical Oncology* Editorial Board consists of 316 members, representing a team of worldwide experts in oncology. They are from 33 countries, including Australia (6), Belgium (2), Brazil (1), Canada (5), China (34), Egypt (2), Finland (1), France (4), Germany (14), Greece (7), Hungary (1), India (5), Iran (1), Israel (2), Italy (27), Japan (20), Malaysia (1), Mexico (1), Netherlands (6), New Zealand (1), Peru (1), Poland (1), Portugal (4), Saudi Arabia (1), Singapore (9), South Korea (7), Spain (7), Sweden (1), Switzerland (2), Thailand (2), Turkey (6), United Kingdom (11), and United States (123).

Robert Mandic, *Marburg*
Klaus Mross, *Freiburg*
Lars Mueller, *Kiel*
Katharina Pachmann, *Jena*
Matthias Peiper, *Düsseldorf*
Gerd J Ridder, *Freiburg*
Harun M Said, *Wuerzburg*

Greece

Leonidas Duntas, *Athens*
Nicholas Pavlidis, *Ioannina*
Professor A Polyzos, *Athens*
Alexander D Rapidis, *Athens*
Evangelia Razis, *Athens*
Dimitrios Roukos, *Ioannina*
Kostas Syrigos, *Athens*

Hungary

Zsuzsa Schaff, *Budapest*

India

Tanya Das, *Kolkata*
G Arun Maiya, *Manipal*
Ravi Mehrotra, *Allahabad*
Sanjeeb K Sahoo, *Bhubaneswar*
Sarwat Sultana, *New Delhi*

Iran

Ali Kabir, *Tehran*

Israel

Avi Hefetz Khafif, *Tel-Aviv*
Doron Kopelman, *Caesarea*

Italy

Luca Arcaini, *Pavia*
Enrico Benzoni, *Tolmezzo*
Rossana Berardi, *Ancona*
Valentina Bollati, *Milan*
Emilio Bria, *Rome*
Guido Cavaletti, *Monza*
Paolo Chieffi, *Naples*
Marco Ciotti, *Rome*
Giuseppe G Di Lorenzo, *Naples*
Alfio Ferlito, *Udine*
Daris Ferrari, *Abbiategrasso*
Alessandro Franchi, *Florence*
Gennaro Galizia, *Naples*
Roberto Mazzanti, *Firenze*
Michele N Minuto, *Pisa*
Simone Mocellin, *Padova*
Nicola Normanno, *Naples*
Marco G Paggi, *Rome*
Domenico Rubello, *Rovigo*
Antonio Russo, *Palermo*
Daniele Santini, *Rome*
Bruna Scaggiante, Trieste
Riccardo Schiavina, *Bologna*
Enzo Spisni, *Bologna*
Bruno Vincenzi, *Rome*
Giovanni Vitale, *Cusano Milanino*

Japan

Hidefumi Aoyama, *Niigata*
Takaaki Arigami, *Kagoshima*
Narikazu Boku, *Shizuoka*
Kazuaki Chikamatsu, *Chuo*
Toru Hiyama, *Higashihiroshima*
Satoru Kakizaki, *Gunma*
Shuichi Kaneko, *Kanazawa*
Koji Kawakami, *Kyoto*
Hiroki Kuniyasu, *Kashihara*
Eiji Miyoshi, *Suita*
Toru Mukohara, *Kobe*
Atsushi Nakajima, *Tokyo*
Takahide Nakazawa, *Sagamihara*
Seishi Ogawa, *Tokyo*
Youngjin Park, *Chiba prefecture*
Naoya Sakamoto, *Tokyo*
Hidekazu Suzuki, *Tokyo*
Michiko Yamagata, *Shimotsuga-gun*
Hiroki Yamaue, *Wakayama*

Malaysia

Min-Tze Liong, *Penang*

Mexico

Rafael Moreno-Sanchez, *Mexico*

Netherlands

Jurgen J Futterer, *Nijmegen*
Bart M Gadella, *Utrecht*
Johannes A Langendijk, *Groningen*
IM Verdonck-de Leeuw, *Amsterdam*
J Voortman, *Amsterdam*

New Zealand

Joanna Skommer, *Auckland*

Peru

Henry L Gomez, *Lima*

Poland

Lukasz Wicherek, *Bydgoszcz*

Portugal

Antonio Araujo, *Porto*
Rui M Medeiros, *Porto*
Paula Ravasco, *Lisbon*
Rui Manuel Reis, *Braga*

Saudi Arabia

Shahab Uddin, *Riyadh*

Singapore

Wei Ning Chen, *Singapore*
John M Luk, *Singapore*
Shu Wang, *Singapore*
Celestial Yap, *Singapore*
Khay-Guan Yeoh, *Singapore*
George W Yip, *Singapore*
Yong Zhang, *Singapore*
Zhan Zhang, *Singapore*

South Korea

Ho-Seong Han, *Seoul*
Young-Seoub Hong, *Busan*
Ja Hyeon Ku, *Seoul*
Geon Kook Lee, *Goyang-si*
Jae Cheol Lee, *Seoul*
Woo Sung Moon, Jeonju
Hyun Ok Yang, *Gangeung*

Spain

Maurizio Bendandi, *Pamplona*
Joan Carles, *Barcelona*
Javier Cortés Castán, *Barcelona*
Jose M Cuezva, *Madrid*
Jesús Prieto, *Pamplona*

Sweden

Lalle Hammarstedt, *Stockholm*

Switzerland

A Lugli, *Basel*
Jacqueline Schoumans, *Lausanne*

Thailand

Suebwong Chuthapisith, *Bangkok*
Songsak Petmitr, *Bangkok*

Turkey

Nejat Dalay, *Istanbul*
Seher Demirer, *Ankara*
Zafer Özgür Pektaş, *Adana*
Alper Sevinc, *Gaziantep*
Engin Ulukaya, *Gorukle Bursa*
Isik G Yulug, *Ankara*

United Kingdom

Shahriar Behboudi, *London*
Alastair David Burt, *Newcastle*

WJCO
World Journal of Clinical Oncology

Contents

Monthly Volume 3 Number 1 January 10, 2012

World Journal of Clinical Oncology
Volume 3 Number 1 January 10, 2012

Contents

NAME OF JOURNAL
World Journal of Clinical Oncology

ISSN
ISSN 2218-4333 (online)

LAUNCH DATE
November 10, 2010

FREQUENCY
Monthly

EDITING
Editorial Board of *World Journal of Clinical Oncology*
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381892
Fax: +86-10-85381893
E-mail: wjco@wjgnet.com
http://www.wjgnet.com

EDITOR-IN-CHIEF
Stuart K Calderwood, PhD, Associate Professor, **Director** Molecular and Cellular Radiation Oncology, Department of Radiation Oncology, Beth Israel Deaconess Medical Center, Harvard Medical School, 99 Brookline Avenue, Boston, MA 02215, United States

EDITORIAL OFFICE
Xiao-Cui Yang, Assistant Director
World Journal of Clinical Oncology
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381892
Fax: +86-10-85381893
E-mail: wjco@wjgnet.com
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Co., Limited
Room 1701, 17/F, Henan Building,
No.90 Jaffe Road, Wanchai, Hong Kong, China
Fax: +852-31158812
Telephone: +852-58042046
E-mail: bpg@baishideng.com
http://www.wjgnet.com

PUBLICATION DATE
January 10, 2012

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/2218-4333/g_info_20100722172206.htm

ONLINE SUBMISSION
http://www.wjgnet.com/2218-4333office/

World Journal of Clinical Oncology

Online Submissions: http://www.wjgnet.com/2218-4333office
wjco@wjgnet.com
doi:10.5306/wjco.v3.i1.1

World J Clin Oncol 2012 January 10; 3(1): 1-6
ISSN 2218-4333 (online)

OBSERVATION

Serendipity in anticancer drug discovery

Emily Hargrave-Thomas, Bo Yu, Jóhannes Reynisson

Emily Hargrave-Thomas, Auckland Bioengineering Institute, The University of Auckland, Auckland 1142, New Zealand
Bo Yu, Jóhannes Reynisson, School of Chemical Sciences, The University of Auckland, Auckland 1142, New Zealand
Author contributions: Hargrave-Thomas E collected and analysed the data and wrote the manuscript; Yu B analysed the data; Reynisson J provided scientific supervision.
Correspondence to: Dr. Jóhannes Reynisson, School of Chemical Sciences, The University of Auckland, Private Bag 92019, Auckland 1142, New Zealand. j.reynisson@auckland.ac.nz
Telephone: +64-9-3737599 Fax: +64-9-3737422
Received: September 22, 2011 Revised: December 19, 2011
Accepted: January 7, 2012
Published online: January 10, 2012

Abstract

It was found that the discovery of 5.8% (84/1437) of all drugs on the market involved serendipity. Of these drugs, 31 (2.2%) were discovered following an incident in the laboratory and 53 (3.7%) were discovered in a clinical setting. In addition, 263 (18.3%) of the pharmaceuticals in clinical use today are chemical derivatives of the drugs discovered with the aid of serendipity. Therefore, in total, 24.1% (347/1437) of marketed drugs can be directly traced to serendipitous events confirming the importance of this elusive phenomenon. In the case of anticancer drugs, 35.2% (31/88) can be attributed to a serendipitous event, which is somewhat larger than for all drugs. The therapeutic field that has benefited the most from serendipity are central nervous system active drugs reflecting the difficulty in designing compounds to pass the blood-brain-barrier and the lack of laboratory-based assays for many of the diseases of the mind.

Key words: Anticancer drugs; Drug discovery and development; Serendipity

Peer reviewers: Arianna L Kim, PhD, Herbert Irving Assistant Professor of Dermatology, Department of Dermatology, Columbia Medical Center, 1130 St. Nicholas Ave 321B, New York, NY 10032, United States; Shufeng Zhou, MD, PhD, A/Professor, School of Health Sciences, RMIT University, Bundoora, Victoria 3083, Australia

Hargrave-Thomas E, Yu B, Reynisson J. Serendipity in anticancer drug discovery. *World J Clin Oncol* 2012; 3(1): 1-6 Available from: URL: http://www.wjgnet.com/2218-4333/full/v3/i1/1.htm DOI: http://dx.doi.org/10.5306/wjco.v3.i1.1

INTRODUCTION

It is well know that serendipity has played a pivotal role in the discovery of many drugs used today[1-3]. Indeed two major classes of anticancer drugs were discovered with the aid of serendipity, i.e., Barnett Rosenberg's discovery of cisplatin and the breakthrough observation by Lieutenant Colonel Stewart F Alexander that the chemical warfare agent, nitrogen mustard, depleted white blood cell numbers; aiding in the development of alkylation agents[1-2]. The question therefore emerges of how important serendipity really is in drug discovery and development? The aim of this investigation is to identify all marketed drugs and their derivatives used in the clinic today in which discovery was in some way based on or aided by a serendipitous event. The numbers obtained will be compared to the total number of marketed drugs resulting in a quantitative measure of the impact of serendipity in the discovery of pharmaceuticals, and anticancer drugs in particular.

METHODOLOGY

Three books were analysed: Laughing Gas, Viagra, and Lipitor: The Human Stories Behind the Drugs We Use[1], Happy Accidents: Serendipity in Modern Medical Breakthroughs[2] and Drug Discovery, a History[3]. Furthermore, one scientific paper was identified with a list of drugs discovered by the aid of serendipity[4]. The books and the paper are shown in Table 1. These resources were studied and the stories containing serendipitous

Table 1 The sources used to identify serendipitous discoveries in drug development

Titles	Authors
Laughing Gas, Viagra, and Lipitor: The Human Stories Behind the Drugs We Use	Li[1]
Happy Accidents: Serendipity in Modern Medical Breakthroughs	Meyers[2]
Drug Discovery, a History	Sneader[3]
Chance favors the prepared mind-from serendipity to rational drug design	Kubinyi[4]

events were recorded. The nature of the serendipitous findings were categorised as laboratory based or clinical. The drugs identified were reviewed in DrugBank[5-7] and only those that were approved, were small molecules, and in clinical use were included. Furthermore, drugs with similar chemical structures and with the same notation (i.e., used to treat the same condition) as the parent drug were considered to be their derivatives as identified by substructure and Tanimoto similarity searching in DrugBank[5-7]. A full list of the drugs found is given in Supplementary Information Tables 2 and 3.

SERENDIPITY IN DRUG DISCOVERY

Serendipity refers to chance discoveries that have been exploited with sagacity[3]. This requires both a chance event and the mental ability to understand the occurrence and realise its potential. In this work, only stories that fit both requirements for serendipity were recorded. The serendipitous events were divided into two categories; laboratory based and clinical. A classic example of the former is Barnett Rosenberg's discovery of cisplatin, and for the latter dimenhydrinate (Dramamine), which was developed as an antihistamine but is now sold as a travel sickness medication due to a chance observation/realisation by one of the participants in the clinical trials. The division of the drugs into these two categories is not always obvious, but we believe that it helps in the analysis of the results. In his book, Serendipity, Roberts[8] coined the term pseudoserendipity to describe accidental discoveries of ways to achieve an end sought for in contrast to the meaning of true serendipity, which describes accidental discoveries of things not sought for. Certainly all of the drugs discovered in the clinic can be described as pseudoserendipitous according to this definition and many of the drugs found in the laboratory.

To calculate the proportion of drugs with a serendipitous background, the total number of small molecule drugs on the market (FDA approved) is taken to be 1437 according to DrugBank[5-7]. Overington *et al*[9] reported 1204 small molecule drugs in clinical use, which is a somewhat smaller number.

In this analysis, 84 drugs were identified to have serendipitous events aiding their discovery, which is 5.8% of all drugs currently in use. Thirty-one drugs (2.2%) were identified in the laboratory and 116 derivatives (8.1%) of

Table 2 List of drugs discovered by serendipitous events in the laboratory and their derivatives

Serendipitous drugs	Derivatives	No. of derivatives
Acetanilide	Acetaminophen	1
Acetohexamide	Tolbutamide, glimepiride, glibenclamide, glipizide, chlorpropamide, gliquidone, tolazamide, gliclazide	8
Captopril	Ramipril, fosinopril, lisinopril, trandolapril, enalapril, perindopril, spirapril, quinapril	8
Cisplatin	Oxaliplatin, carboplatin	2
Diethylstilbestrol	Dienestrol	1
Digoxin	Digitoxin, deslanoside, acetyldigitoxin, ouabain	4
Ergotamine	Dihydroergotamine, dihydroergotoxine, ergoloidmesylate, methysergide, methylergonovine, ergonovine	6
Ephedrine	Pseudoephedrine, ritodrine, metaraminol, phenylephrine, isoetharine, fenoterol, epinephrine, orciprenaline, terbutaline	9
Griseofulvin	NA	0
Heparin	Pentosan, polysulfate, enoxaparin, ardeparin, fondaparinux sodium	4
Isoniazid	NA	0
Lidocaine	Prilocaine, tocainide, mepivacaine, bupivacaine, levobupivacaine, ropivacaine	6
Lithium	NA	0
Marinol	Nabilone	1
Mechlorethamine	Chlorambucil, cyclophosphamide, melphalan, uracil mustard, estramustine	5
Mecillinam	Pivmecillinam	1
Methotrexate	Leucovorin	1
Nalidixic acid	Rosoxacin, enoxacin, pefloxacin, norfloxacin, lomefloxacin, ciprofloxacin, levofloxacin, ofloxacin	8
Nitroglycerine	ErythritylTetranitrate, IsosorbideDinitrate	2
Penicillin	Ampicillin, amoxicillin, azidocillin, azlocillin, bacampicillin, carbenicillin, cloxacillin, cyclacillin, dicloxacillin, flucloxacillin, hetacillin, meticillin, mezlocillin, nafcillin, oxacillin, penicillin g, penicillin v, piperacillin, pivampicillin, tazobactam, ticarcillin	21
Pentamidine	NA	0
Physostigmine	NA	0
Quinine	Quinidine	1
Sorafenib	NA	0
Streptomycin	Framycetin, neomycin, josamycin, tobramycin, kanamycin, candicidin, spectinomycin	7
Sulfanilamide	Silver sulfadiazine, sulfacetamide, sulfacytine, sulfadiazine, sulfadimethoxine, sulfadoxine, sulfamerazine, sulfamethizole, sulfametopyrazine, sulfamethoxazole, sulfamoxole, sulfapyridine, sulfisoxazole	13
Valproic acid	Divalproex sodium	1
Vinblastine	Vincristine, vindesine, vinorelbine	3
Dicoumarol	NA	0
Warfarin	Acenocoumarol, phenprocoumon, dicumarol	3
Zinc Sulfate	NA	0

NA: Not available.

Table 3 List of drugs discovered to be beneficial for conditions other than for which they were developed (clinical)

Off-label drugs	Derivatives	No. of derivatives
Aminoglutethimide	NA	0
Alprostadil	Dinoprostone, carboprost, tromethamine, dinoprost, tromethamine, misoprostol	4
Amphetamine	Phentermine, methamphetamine, dextroamphetamine, alverine, selegiline, mephentermine, tranylcypromine, phenelzine, benzphetamine, diethylpropion	10
Aspirin	NA	0
Auranofin	NA	0
Carbamazepine	Oxcarbazepine	1
Celecoxib	NA	0
Chlordiazepoxide	Diazepam, temazepam, oxazepam, fludiazepam, clorazepate, halazepam, prazepam, flurazepam, lorazepam, cinolazepam, clonazepam, nitrazepam, bromazepam, flunitrazepam, quazepam, clotiazepam, alprazolam, estazolam, adinazolam, midazolam	20
Chlorothiazide	Benzthiazide, diazoxide, hydrochlorothiazide, hydroflumethiazide, bendroflumethiazide, cyclothiazide, polythiazide, trichlormethiazide, methyclothiazide, furosemide, bumetanide	11
Clofibrate	Fenofibrate	1
Dactinomycin	NA	0
Diisopropylfluorophosphate	NA	0
Diltiazem	NA	0
Dimenhydrinate	NA	0
Diphenhydramine	Bromodiphenhydramine, diphenylpyraline	2
Diphenoxylate	Loperamide	1
Dipyridamole	NA	0
Disulfiram	NA	0
Doxorubicin	Epirubicin, daunorubicin, idarubicin, valrubicin, plicamycin	5
Etomidate	NA	0
Finasteride	Dutasteride	1
Guanethidine	Debrisoquin, guanidine	2
Haloperidol	Droperidol	1
Imatinib	NA	0
Imipramine	Trimipramine, desipramine, clomipramine, protriptyline, amitriptyline, nortriptyline, cyclobenzaprine, maprotiline, doxepin, Amoxapine	10
Iproniazid	Isocarboxazid	1
Linezolid	NA	0
Lysergic Acid Diethylamide	Cabergoline, lisuride, bromocriptine, nicergoline, pergolide	5
Meprobamate	Carisoprodol	1
Mercaptopurine	Thioguanine, azathioprine	2
Metronidazole	Tinidazole	1
Mifepristone	NA	0
Minoxidil	NA	0
Mycophenolic acid	Mycophenolatemofetil	1
Naloxone	Naltrexone	1
Norethindrone	Levonorgestrel, norgestrel, etonogestrel, gestodene,desogestrel, medroxyprogesterone, megestrol, progesterone, drospirenone, norelgestromin, ethynodioldiacetate	11
Pethidine	Anileridine	1
Phenobarbital	Methylphenobarbital, secobarbital, metharbital, aprobarbital, primidone, methsuximide	6
Prednisone	Medrysone, methylprednisolone, prednisolone, rimexolone, fluocortolone, desoximetasone	6
Probenecid	NA	0
Procarbazine	NA	0
Promethazine	Acepromazine, aceprometazine, acetophenazine, arphenazine, chlorpromazine, ethopropazine, fluphenazine, mesoridazine, methotrimeprazine, perphenazine, pipotiazine, prochlorperazine, promazine, propericiazine, propiomazine, thioproperazine, thioridazine, trifluoperazine, triflupromazine, trimeprazine	20
Quinacrine	Chloroquine, primaquine, hydroxychloroquine, amodiaquine	4
Reserpine	Deserpidine, rescinnamine	2
Salicyclic acid	Salsalate, olsalazine, diflunisal, mesalazine	4
Sildenafil	Tadalafil, vardenafil	2
Sirolimus	Everolimus	1
Tamoxifen	Toremifene	1
Terfenadine	Fexofenadine	1
Thalidomide	Lenalidomide	1
Tolazoline	NA	0
Trimethadione	Paramethadione	1
Zidovudine	Trifluridine, telbivudine, idoxuridine, zalcitabine, stavudine	5

NA: Not available.

Table 4 List of drugs discovered with the aid of serendipity in the laboratory, the number of identified derivatives and their therapeutic notation

Drugs	Ref.	Derivatives	Notation
Acetanilide	[3,4]	1	Antipyretic
Acetohexamide	[1,3,4]	8	Diabetes II
Captopril	[1,3]	8	Cardiovascular
Cisplatin	[1-4]	2	Cancer
Diethylstilbestrol	[3,4]	1	Hormonal
Digoxin	[1,3]	4	Cardiovascular
Ergotamine	[1-3]	6	Cardiovascular
Ephedrine	[3]	9	CNS
Griseofulvin	[3,4]	0	Antifungal
Heparin	[2-4]	4	Cardiovascular
Isoniazid	[3,4]	0	Antibiotic
Lidocaine	[3]	6	CNS
Lithium	[1-4]	0	CNS
Marinol	[3]	1	CNS
Mechlorethamine	[1-4]	5	Cancer
Mecillinam	[3]	1	Antibiotic
Methotrexate	[1,3]	1	Cancer
Nalidixic Acid	[1,3]	8	Antibiotic
Nitroglycerine	[1,3,4]	2	Cardiovascular
Penicillin	[1-4]	21	Antibiotic
Pentamidine	[3]	0	Antiprotozoal
Physostigmine	[3]	0	Ocular
Quinine	[3]	1	Antiprotozoal
Sorafenib	[1]	0	Cancer
Streptomycin	[1,2]	7	Antibiotic
Sulfanilamide	[1-3]	13	Antibiotic
Valproic acid	[3,4]	1	CNS
Vinblastine	[1-3]	3	Cancer
Dicoumarol	[2-4]	0	Cardiovascular
Warfarin	[2-4]	3	Cardiovascular
Zinc Sulfate	[3]	0	Wilson's disease

CNS: Central nervous system.

these drugs were identified as shown in Table 4. Fifty-three pharmaceuticals (3.7%) were discovered in clinical settings and 147 derivatives (10.2%) of these were identified (Table 4). Therefore, in total there are 347 drugs currently on the market, in which discovery was aided by a serendipitous event, representing a staggering 24.1% of all drugs currently on the market. A graphical representation of these results is shown in Figure 1.

SERENDIPITY IN ANTICANCER DRUG DISCOVERY AND DEVELOPMENT

According to DrugBank[5-7] there are 88 anticancer drugs in clinical use today. Of the drugs identified with serendipitous origin, 13 are used to treat cancer and 18 are their chemical derivatives. This means that 35.2% of all anticancer drugs in clinical use involved serendipity of some kind. The statistical distribution is shown in Figure 2. This represents a larger portion of serendipitous effects than for pharmaceuticals in general.

Of the primary serendipitous events, anticancer drugs represent 15.5% (13/84), i.e., a sizeable portion. However, relatively few derivatives were found for anticancer drugs (6.8% of the derivatives). This highlights

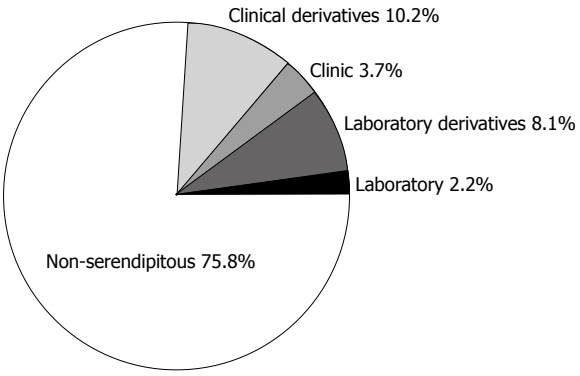

Figure 1 The distribution of the serendipity types (laboratory-based and clinical) and their chemical derivatives in clinical use (100% = 1437).

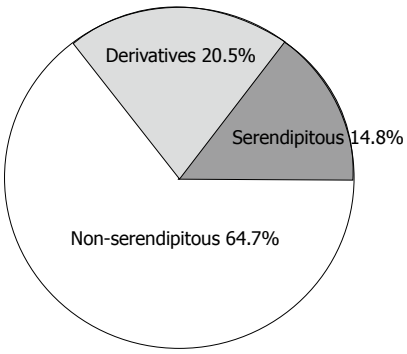

Figure 2 The statistical distribution of anticancer drugs discovered with the aid of serendipity and their chemical derivatives in clinical use (100% = 88).

the difficulty in developing effective anticancer drugs.

When the primary serendipitous events are investigated, it is clear that antibiotic, anticancer, cardiovascular and central nervous system (CNS) drugs are the most common notations with about 10 events for each (Tables 4 and 5). Other therapeutic fields such as antiprotozoal and antifungal are also reported. Less common treatments for conditions such as gout and alcoholism are reported. A high frequency of CNS discoveries is seen in the clinical settings in Table 4, i.e., 17 out of a total of 53. This reflects the difficulty in developing drugs that need to pass the Blood-Brain-Barrier (e.g., reference[10] and references therein), and the dearth of biochemical assays modelling the diseases of the mind and pain.

KNOWN DRUG SPACE

Recently a new concept of Known Drug Space (KDS) has been developed to help drug designers to navigate chemical space based on the analysis of drugs in clinical use[11-13]. It is known that 10% of KDS are unaltered natural products and 29% are their derivatives (semi-synthetics)[14]. With this fact and the results presented in this paper it can be stated that KDS is, to a large extent, populated by chance rather than design. Therefore, the analysis of the physicochemical properties of known drugs gives a region of property space that really works

Table 5 List of drugs found to be beneficial for conditions other than for which they were developed (clinical), the number of identified derivatives and their therapeutic notation

Clinical drugs	Ref.	Derivatives	Notation
Aminoglutethimide	[3,4]	0	Cancer
Alprostadil	[3]	4	Cardiovascular
Amphetamine	[1,3,4]	10	CNS
Aspirin	[1-3]	0	Cardiovascular/Cancer
Auranofin	[2,3]	0	Antirheumatic
Carbamazepine	[3]	1	CNS
Celecoxib	[2]	0	Cancer
Chlordiazepoxide	[1-4]	20	CNS
Chlorothiazide	[1,3,4]	11	Diuretic
Clofibrate	[3]	1	Cardiovascular
Dactinomycin	[3]	0	Cancer
Diisopropylfluorophosphate	[3]	0	Ocular
Diltiazem	[3]	0	Cardiovascular
Dimenhydrinate	[2-4]	0	CNS
Diphenhydramine	[3]	2	CNS
Diphenoxylate	[3,4]	1	Antidiarrheal
Dipyridamole	[3]	0	Cardiovascular
Disulfiram	[1,2,4]	0	Alcoholism treatment
Doxorubicin	[3]	5	Cancer
Etomidate	[3,4]	0	CNS
Finasteride	[2]	1	Baldness
Guanethidine	[3,4]	2	Cardiovascular
Haloperidol	[1,3,4]	1	CNS
Imatinib	[1]	0	Cancer
Imipramine	[1-4]	10	CNS
Iproniazid	[1-4]	1	CNS
Linezolid	[1]	0	Antibiotic
LSD	[1-4]	5	CNS
Meprobamate	[2,4]	1	CNS
Mercaptopurine	[1,3]	2	Immunosuppressive
Metronidazole	[3]	1	Antiprotozoal
Mifepristone	[3,4]	0	Hormonal
Minoxidil	[2]	0	Cardiovascular
Mycophenolic acid	[3]	1	Immunosuppressive
Naloxone	[3]	1	CNS
Norethindrone	[1,3,4]	11	Hormonal
Pethidine	[3,4]	1	CNS
Phenobarbital	[3]	6	CNS
Prednisone	[3,4]	6	Anti-inflammatory
Probenecid	[2]	0	Gout
Procarbazine	[3]	0	CNS
Promethazine	[1-3]	20	Antihistamine
Quinacrine	[3]	4	Antiprotozoal
Reserpine	[1-3]	2	CNS
Salicyclic acid	[3]	4	Antirheumatic
Sildenafil	[1-3]	2	Erectile dysfunction
Sirolimus	[3]	1	Immunosuppressive
Tamoxifen	[1-4]	1	Cancer
Terfenadine	[3]	1	Antihistamine
Thalidomide	[1,2]	1	Cancer
Tolazoline	[3]	0	Cardiovascular
Trimethadione	[3]	1	CNS
Zidovudine	[1,2]	5	Antiviral

CNS: Central nervous system; LSD: Lysergische säure diäthylamid (lysergic acid diethylamide).

for successful pharmaceuticals.

DISCUSSION

Serendipity in drug discovery has not been investigated to a great extent, however, some papers were found in the literature and the opinions expressed vary greatly, which is not surprising due to the ambiguous nature of this phenomenon. For instance, Jeste *et al*[15] downplay the importance of serendipity arguing that few if any discoveries in their field of psychiatry were truly serendipitous. Conversely, Lombardino and Lowe state that "the role of serendipity, chemical intuition and creativity in thoughtfully selecting a chemical target to synthesize in order to discover the best-quality drug has not diminished" irrespective of the introduction of new technologies[16]. Furthermore, Klein strongly believes that a loss of chance observations and unexpected clinical benefits are due to recent changes in the process of drug discovery[17]. He criticises cost-control measures which remove a creative environment in hospitals that fosters serendipity[17]. Finally, Kubinyi[4] suggests that researchers should not be manipulated by short-term business cycles; drug discoveries require good science, enlightened management, and freedom for researchers to act, challenge dogma and take risks.

This investigation provides a limited scope of serendipitous drug discovery since only four sources were analysed. It is certain that not all serendipitous events are recorded; researchers may choose not to report them in favour of standard scientific methods of inquiry. It can therefore be argued that the impact of serendipity is even larger than found in this investigation.

According to the results presented here, approximately 24% of all drugs currently on the market were discovered with the aid of serendipity and thus, may never have been discovered without the curiosity, observation, and sagacity of the researchers. This serves to highlight the unpredictability in drug research and the necessity to allow for and encourage freedom in research directions and promote the intellectual freedom of the scientists involved. Also, a sound education in science is indispensable and the promotion of critical thinking of our students is vital (for further discussion see Lenox[18]).

The term "drug repositioning" is sometimes used when a new notation is found for a drug molecule. A good example is the reintroduction of the infamous thalidomide in clinical use. This is obviously a very positive development since new drugs do not have to be developed from scratch with a large price tag. As shown in this work, serendipitous events in the clinic are important and have facilitated drug repositioning emphasising the need to educate clinicians about this phenomenon.

Understanding the serendipity phenomenon is crucial so we can start to manipulate it to our advantage and we believe that quantifying the impact of serendipity facilitates our understanding of it. Finally, Pasteur's comment on serendipity certainly still holds true: "Dans les champs de l'observation, le hasard ne favoriseque les esprits prepares." ("In the field of observation, chance favours only the prepared mind.")

CONCLUSION

It was found that 35.2% of all the anticancer drugs now

in clinical use were discovered by serendipity. In general, 24% of all pharmaceuticals currently on the market were affected in a positive way during their development by this phenomenon with CNS active drugs being the most prominent. This leads to the conclusion that drug discovery is based on good science and where intuition, critical thinking, sagacity and open-mindedness play crucial roles.

REFERENCES

1 **Li JJ**. Laughing Gas, Viagra and Lipitor The human Stories Behind the Drugs We Use. Oxford: Oxford University Press, 2006
2 **Meyers MA**. Happy Accidents Serendipity in Modern Medical Breakthroughs. New York: Arcade Publishing, 2007
3 **Sneader W**. Drug Discovery a History. Chichester: John Wiley and Sons Ltd., 2005
4 **Kubinyi H**. Chance favors the prepared mind--from serendipity to rational drug design. *J Recept Signal Transduct Res* 1999; **19**: 15-39
5 **Wishart DS**, Knox C, Guo AC, Cheng D, Shrivastava S, Tzur D, Gautam B, Hassanali M. DrugBank: a knowledgebase for drugs, drug actions and drug targets. *Nucleic Acids Res* 2008; **36**: D901-D906
6 **Wishart DS**, Knox C, Guo AC, Shrivastava S, Hassanali M, Stothard P, Chang Z, Woolsey J. DrugBank: a comprehensive resource for in silico drug discovery and exploration. *Nucleic Acids Res* 2006; **34**: D668-D672
7 **Knox C**, Law V, Jewison T, Liu P, Ly S, Frolkis A, Pon A, Banco K, Mak C, Neveu V, Djoumbou Y, Eisner R, Guo AC, Wishart DS. DrugBank 3.0: a comprehensive resource for 'omics' research on drugs. *Nucleic Acids Res* 2011; **39**: D1035-D1041
8 **Roberts RM**. Serendipity Accidental Discoveries in Science. New York: Wiley Science Editions, 1989
9 **Overington JP**, Al-Lazikani B, Hopkins AL. How many drug targets are there? *Nat Rev Drug Discov* 2006; **5**: 993-996
10 **King A**. Breaking through the barrier. *Chemistry World* 2011: 36-39
11 **Ioakimidis L**, Thoukydidis L, Naeem S, Mirza A, Reynisson J. Benchmarking the Reliability of QikProp. Correlation between Experimental and Predicted Values. *QSAR Comb Sci* 2008; **27**: 445-456
12 **Axerio-Cilies P**, Castañeda IP, Mirza A, Reynisson J. Investigation of the incidence of "undesirable" molecular moieties for high-throughput screening compound libraries in marketed drug compounds. *Eur J Med Chem* 2009; **44**: 1128-1134
13 **Mirza A**, Desai R, Reynisson J. Known drug space as a metric in exploring the boundaries of drug-like chemical space. *Eur J Med Chem* 2009; **44**: 5006-5011
14 **Bade R**, Chan HF, Reynisson J. Characteristics of known drug space. Natural products, their derivatives and synthetic drugs. *Eur J Med Chem* 2010; **45**: 5646-5652
15 **Jeste DV**, Gillin JC, Wyatt RJ. Serendipity in biological psychiatry--a myth? *Arch Gen Psychiatry* 1979; **36**: 1173-1178
16 **Lombardino JG**, Lowe JA. The role of the medicinal chemist in drug discovery--then and now. *Nat Rev Drug Discov* 2004; **3**: 853-862
17 **Klein DF**. The loss of serendipity in psychopharmacology. *JAMA* 2008; **299**: 1063-1065
18 **Lenox RS**. Educating for the Serendipitous Discovery. *J Chem Edu* 1985; **62**: 282-285

S- Editor Yang XC **L- Editor** Webster JR **E- Editor** Li JY

World Journal of Clinical Oncology

Online Submissions: http://www.wjgnet.com/2218-4333office
wjco@wjgnet.com
doi:10.5306/wjco.v3.i1.7

World J Clin Oncol 2012 January 10; 3(1): 7-11
ISSN 2218-4333 (online)

CASE REPORT

Challenges in the differential diagnosis of hypercalcemia: A case of hypercalcemia with normal PTH level

Francesca Pellicciotti, Andrea Giusti, Maria Carolina Gelli, Salvatore Foderaro, Alberto Ferrari, Giulio Pioli

Francesca Pellicciotti, Salvatore Foderaro, Alberto Ferrari, Giulio Pioli, Geriatric Unit, Arcispedale Santa Maria Nuova, Viale Risorgimento 80, 42123 Reggio Emilia, Italy
Andrea Giusti, Bone Clinic, Department of Gerontology and Musculoskeletal Sciences, Galliera Hospital, Corso Mentana 10, 16128 Genoa, Italy
Maria Carolina Gelli, Department of Pathology, Arcispedale Santa Maria Nuova, Viale Risorgimento 80, 42123 Reggio Emilia, Italy
Author contributions: All authors contributed to conception and design, acquisition and interpretation of data; Francesca Pellicciotti, Andrea Giusti and Giulio Pioli contributed equally to the drafting of the article; Maria Carolina Gelli, Salvatore Foderaro, Alberto Ferrari and Giulio Pioli revised the article critically for important intellectual content; all authors approved the final version to be published.
Correspondence to: Giulio Pioli, MD, Geriatric Unit, Arcispedale Santa Maria Nuova, Viale Risorgimento 80, 42123 Reggio Emilia, Italy. giulio.pioli@asmn.re.it
Telephone: +39-052-2296188 Fax: +39-052-2296122
Received: August 10, 2011 Revised: October 21, 2011
Accepted: January 7, 2012
Published online: January 10, 2012

Abstract

The hypercalcemias are a common and heterogeneous group of disorders, ranging from the occasional detection of a high level of serum calcium to a life-treating condition. In a patient presenting with hypercalcemia, a differential diagnosis can be established easily by measuring serum calcium and parathyroid hormone (PTH) concentrations. We describe the case of an 83-year-old man presenting with a severe symptomatic hypercalcemia with high-normal PTH level due to the coexistence of primary hyperparathyroidism and malignancy-associated hypercalcemia. The presence of two conditions producing hypercalcemia was revealed only during in-hospital stay and after the administration of an intravenous bisphosphonate, when the PTH concentration increased rapidly after bisphosphonate treatment with a decrease in serum calcium. The occurrence of two conditions producing hypercalcemia is a rare event in the literature, and should be considered in the presence of an abnormally high serum calcium level associated with normal or high-normal PTH, in order to establish a correct diagnosis and appropriate interventions.

Key words: Bisphosphonates; Hypercalcemia; Malignancy-associated hypercalcemia; Parathyroid hormone; Primary hyperparathyroidism

Peer reviewer: Tim Van den Wyngaert, Dr., Antwerp University Hospital, Wilrijkstraat 10, 2650 Edegem, Belgium

Pellicciotti F, Giusti A, Gelli MC, Foderaro S, Ferrari A, Pioli G. Challenges in the differential diagnosis of hypercalcemia: A case of hypercalcemia with normal PTH level. *World J Clin Oncol* 2012; 3(1): 7-11 Available from: URL: http://www.wjgnet.com/2218-4333/full/v3/i1/7.htm DOI: http://dx.doi.org/10.5306/wjco.v3.i1.7

INTRODUCTION

The hypercalcemias (HCa) are a common and heterogeneous group of disorders, ranging from the occasional detection of a high level of serum calcium during routine laboratory assessment to a life-treating condition[1-5]. In general, the signs and symptoms are not specific, and are related to the level of serum calcium, to the rate of calcium increase and to the underlying condition producing HCa. Mild hypercalcemia (11-11.5) mg/dL is usually asymptomatic, while acute onset severe HCa (> 13 mg/dL) may present with lethargy, stupor and coma.

From a pathophysiological point of view, an increase in serum calcium above the reference range is the result of the failure of renal calcium excretion to compensate for an increased influx of calcium into the circulation from the intestine, the kidneys and the skeleton[4,5]. Primary hyperparathyroidism and malignant neoplasms are

responsible for more than 90% of all cases of hypercalcemia[5].

In the case of hypercalcemia, a differential diagnosis can be established easily by measuring serum calcium and parathyroid hormone (PTH) concentrations. In clinical practice, serum total calcium concentrations should be adjusted to serum albumin values, while the measurement of ionized serum calcium is rarely needed[4,5].

The finding of an increased serum calcium level in the presence of an inappropriately elevated PTH concentration should suggest a PTH-dependent HCa (primary hyperparathyroidism), while the observation of HCa with suppressed or low-normal PTH values should suggest a PTH-independent hypercalcemia (e.g., granulomatous disorders or malignancy-associated hypercalcemia, MAH)[1,2,4,5].

In the acute clinical setting, the management of severe HCa is independent of the underlying cause, being based on life-treating interventions such as hydration and the prescription of calcium lowering agents (e.g., bisphosphonates). On the other hand, the long-term treatment and prognosis of HCa is highly dependent on the underlying cause[4]. Therefore, a correct differential diagnosis is crucial to maximize the outcome and improve quality of life.

We herein describe the case of an 83-year-old man presenting with hypercalcemia with normal PTH level due to the coexistence of primary hyperparathyroidism and MAH. The occurrence of two conditions producing HCa is a rare event in the literature[6-8], and should be considered in the presence of an abnormally high serum calcium level associated with normal PTH, in order to establish a correct diagnosis and appropriate interventions.

CASE REPORT

An 83-year-old man was admitted to the Geriatric Acute Care Unit of the Arcispedale Santa Maria Nuova (ASMN, Reggio Emilia) with delirium and other symptoms. The patient was evaluated at the time of admission and followed during hospital stay with serial measurements of laboratory tests.

Serum 25-hydroxy-vitamin D (25-OH-D) was measured by radioimmunoassay using a commercial kit (detection limit 1.5 ng/mL; DiaSorin, Saluggia, Italy). Serum intact PTH (1-84) was assessed using an immunoradiometric method (DiaSorin) with a sensitivity of 0.7 pg/mL (normal range 15 pg/mL-75 pg/mL). The interassay coefficients of variation (CVs) were between 8.2% and 11% for 25-OH-D and between 3.4% and 4.9% for PTH (depending on the measured concentration). All other parameters were measured using standard automated laboratory methods.

A needle biopsy of axillary lymph nodes and a bone marrow biopsy (obtained from the iliac crest) were performed. Specimens were fixed in 4% buffered formaldehyde (bone marrow biopsy was subsequently decalcified) and processed for routine paraffin embedding. Sections of 5 μm were prepared for routine light microscopy after staining with hematoxylin and eosin. Immunohistochemical staining with the streptavidin-biotin peroxidase detection system was performed using the Ventana automated immunostainer (Ventana Medical System, Tucson, Arizona, United States).

The patient was admitted to the Geriatric Acute Care Unit of the ASMN Hospital at the beginning of August 2010. He was an 83-year-old man, living at home with his wife and walking without aid. His medical history included mild to moderate dementia (started one year before) with minor behavioral symptoms, hypertension, chronic coronary heart disease, carotid atheromatous disease, benign prostatic hyperplasia treated with trans-urethral retrograde prostatectomy, chronic gastritis and duodenal ulcer. Despite having dementia and other comorbidities, he had conserved abilities of daily living. Medications included: trazodone 12.5 mg/bid, bisoprolol 1.25 mg/d, losartan 25 mg/d, acetylsalicylic acid 100 mg/d and rosuvastatin 10 mg/d.

Five days before admission to ASMN Hospital, he was evaluated in the Emergency Department of another hospital for asthenia and worsening of cognitive impairment. Routine blood samples and radiologic evaluations (brain CT and abdominal X-ray) showed severe hyponatremia (121 mmol/L), chronic vascular encephalopathy and coprostasis. Serum calcium was not assessed. He was discharged home without any therapy.

On admission to the Geriatric Unit of the ASMN Hospital, his caregiver referred to persistence of the following symptoms: asthenia, dizziness, recurrent falls, drowsiness, delirium, constipation, polyuria, polydipsia and stupor. The first laboratory assessment confirmed the presence of hyponatremia (129 mmol/L), and demonstrated hypocloremia (87 mmol/L), leukocytosis (10.829/mmc), normocytic anemia (Hb 12.2 mg/dL; MCV 81.4) and renal failure (creatinine 1.6 mg/dL; azotemia 46). Chest and abdominal X-rays were negative. The symptoms were, at this point, correlated to hyponatremia and dehydration-syndrome. Thus, fluid and electrolyte therapy were started.

On the second day a routine blood sample showed moderate liver dysfunction, the presence of monoclonal antibodies below the detection limit on serum protein electrophoresis, and severe hypercalcemia (18.2 mg/dL) with PTH (64 pg/mL) within the reference range (Figure 1), associated with hyperphosphatemia (4.8 mg/dL, normal range 2.5 mg/dL-4.5 mg/dL) and hypomagnesemia (1.6 mg/dL, normal range 1.7 mg/dL-2.5 mg/dL).

Given the presence of severe symptomatic hypercalcemia, the patient was treated with re-hydration associated with furosemide, and an intravenous bisphosphonate (pamidronate 60 mg in 500 cc saline in a single administration). As shown in Figure 1, a slight decrease in calcium was observed in the first two days after bisphosphonate treatment, followed by a rapid decrease in serum calcium from day 3. At the same time, PTH demonstrated a rapid and sustained increase in the days following the bisphosphonate infusion (up to 410 pg/mL).

In association with the decrease in serum calcium, a

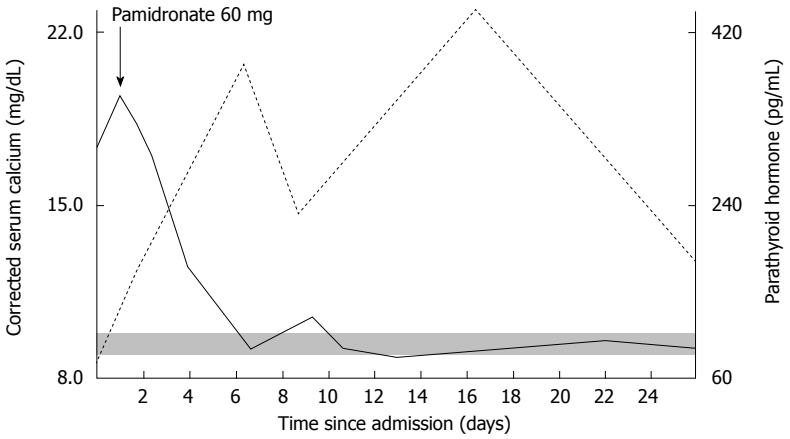

Figure 1 Corrected serum calcium and parathyroid hormone concentrations during hospitalization, before and after pamidronate administration. Continuous line, corrected serum calcium; dotted line, serum parathyroid hormone (10 pg/mL-75 pg/mL); gray band, normal reference range for serum calcium (8.5 mg/dL-10.5 mg/dL).

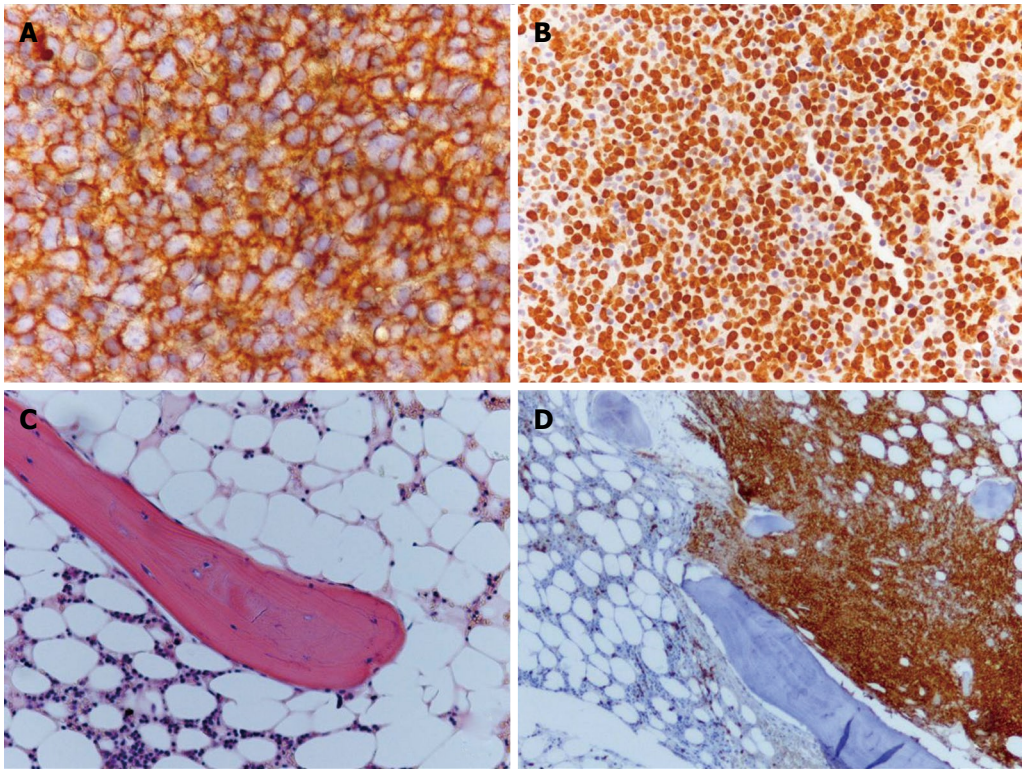

Figure 2 Histological sections of axillary lymph node (A and B) and bone marrow (C and D). Lymph node: A: Immunohistochemical stain for CD20; B: Immunohistochemical stain for Ki67; Bone marrow: C: Hematoxylin-eosin staining; D: Immunohistochemical stain for CD20.

significant improvement in symptoms was observed. In particular, this treatment ameliorated the level of consciousness, resolved dizziness and improved ambulation.

The coexistence of severe symptomatic hypercalcemia with a PTH level within the reference range suggested the presence of two different conditions producing an increase in serum calcium, but opposite effects on PTH (PTH-dependent and PTH-independent hypercalcemia)[1-3].

The sudden increase in PTH (from 64 pg/mL to 410 pg/mL) following the slight decrease in calcium (from 18.2 mg/dL to 15.7 mg/dL; still above the upper limit of the reference range) early after pamidronate infusion, suggested the presence of primary hyperparathyroidism. Further instrumental investigations were undertaken due to a suspected coexisting MAH.

A whole-body bone scan did not detect any areas of increased uptake, and therefore, excluded hypercalcemia due to osteolysis. A whole body CT scan demonstrated the presence of enlarged mediastinal and abdominal lymph nodes suggesting a lymphoproliferative disease. A needle biopsy of axillary lymph nodes was performed. Histological examination revealed a diffuse large B-cell non-Hodgkin lymphoma confirming MAH (Figure 2A and 2B). The examined tissue was completely replaced

by medium to large lymphoid cells with oval to round nuclei. Immunohistochemical investigation revealed a B-cell phenotype (CD20+, Bcl2+, Bcl6+, CD3-, CD10-, CD30-, cyclin D1-). The proliferative fraction detected by Ki67 staining was notably high (80%-90%).

An echographic evaluation of the neck was unable to localize the abnormal parathyroid gland, while a sestamibi scintigraphic evaluation undertaken to localize the hyperfunctioning parathyroid gland demonstrated an area of increased uptake at the base of the right thyroid lobe.

Among the laboratory analyses, a severe vitamin D deficiency was observed. The bone marrow biopsy revealed normal trabecular borders and surface excluding osteomalacia (Figure 2C and D). Cellularity was increased, but hematopoietic marrow lines were reduced. About 70% of bone marrow cellularity was occupied by a lymphoid proliferation, diffusely necrotic with analogous characteristics which were observed in lymph node tissue.

The final diagnosis was non-Hodgkin lymphoma stage 4A associated with primary hyperparathyroidism. When serum calcium was normalized, the patient started chemotherapy. Unfortunately, on the 36th day (six days after the first chemotherapy cycle), the patient's clinical condition worsened and two days later he died due to irreversible heart failure. Thus, it was not possible to undertake further investigations.

DISCUSSION

In clinical practice, the differential diagnosis of hypercalcemia is based on the evaluation of serum calcium and PTH levels, with a high PTH concentration suggesting a PTH-dependent hypercalcemia (usually primary hyperparathyroidism), and a suppressed PTH value supporting the diagnosis of a PTH-independent hypercalcemia (most often a MAH or a calcitriol-excess hypercalcemia)[1-4]. In the case described, the coexistence of severe hypercalcemia with a PTH concentration in the normal reference range suggested a more complex diagnosis.

Among the potential causes of hypercalcemia, granulomatous diseases, familial hypocalciuric hypercalcemia and drug-induced HCa (e.g., lithium) were excluded on the basis of the medical and pharmacological history, and first-line investigations[1-3]. The laboratory assessment, undertaken during in-hospital stay, excluded hyperthyroidism, tertiary hyperparathyroidism and other rare disorders such as milk-alkali syndrome[1-3]. Thus, even on the basis of their higher prevalence, primary hyperparathyroidism and MAH were considered the potential cause of HCa in the 83-year-old man described.

The presence of a really high level of calcium with a PTH value within the reference range suggested the possibility of the coexistence of a primary hyperparathyroidism and another not-PTH-mediated hypercalcemic disorder, which, by increasing serum calcium to a level close to the PTH-secretion set-point, was capable of inhibiting secretion of the parathyroids, thus explaining the "atypical" normal PTH concentration. Apart from the diagnosis of lymphoma, which indirectly supported our hypothesis, the dramatic increase in PTH concentration after the infusion of pamidronate further supported our diagnoses. It is probable that pamidronate, by reducing osteoclast-mediated bone resorption and therefore calcium mobilization from the bone tissue, re-established PTH secretion thus reducing serum calcium and its inhibitory action on the parathyroids.

As we also found severe hypovitaminosis D, we also considered the hypothesis that the presence of a secondary hyperparathyroidism could induce an abnormal level of PTH in the presence of MAH. In fact, it is known that the normalization of PTH in secondary hyperparathyroidism, during supplementation with vitamin D, takes a long time, and that even after one year of treatment some patients still have high levels of PTH. This situation is considered to be related to hyperplasia of the parathyroids or to morphological modifications of these glands produced by the long-lasting hypocalcemic stimulus[9]. However, it is commonly believed that the response of the parathyroid glands to a hypercalcemic stimulus is quite fast and relevant, even in the presence of hyperplastic glands as demonstrated by Messa *et al*[10].

Another potential confounder in the clinical presentation of our case was the low magnesium concentration. Magnesium is essential for PTH secretion, and hypomagnesemia has been shown to blunt PTH increase in conditions such as severe vitamin D deficiency[11,12]. In our case, a rapid and sustained increase in PTH concentration occurred in the absence of magnesium supplementation, suggesting that magnesium deficiency was not the reason for the normal PTH level associated with severe HCa.

Hyponatremia was related to severe dehydration and to loss of urine sodium due to hypercalciuria, and a diagnosis of inappropriate secretion of antidiuretic hormone (trazodone, lymphoma) was excluded. This was also supported by the fact that hyponatremia resolved once the patient was re-hydrated and serum calcium was normalized.

In summary, the case described has some clinical implications: in patients with primary hyperparathyroidism, the coexistence of severe hypercalcemia which is not PTH-mediated, represents a challenge in the differential diagnosis of HCa; therefore, the presence of very high calcium concentrations with normal PTH values should suggest the coexistence of more than one disease producing hypercalcemia; when a patient, specially an older adult, is admitted to an Acute Care Unit or an Emergency Department with worsening cognitive impairment, delirium and asthenia, the calcium concentration should be measured together with routine laboratory and radiologic evaluations.

REFERENCES

1 **Silverber SJ,** Bilezikian JP. Primary hyperparathyroidism. 7th ed. In: Rosen CJ, editor. Primer on the metabolic bone diseases and disorders of mineral metabolism. Washington DC: American Society for Bone and Mineral Research, 2008: 301-306

2 **Horwitz MJ,** Hodak SP, Stewart AF. Non-parathyroid hypercalcemia. 7th ed. In: Rosen CJ, editor. Primer on the metabolic bone diseases and disorders of mineral metabolism. Washington DC: American Society for Bone and Mineral Research, 2008: 307-312

3 **Moe SM**. Disorders involving calcium, phosphorus, and magnesium. *Prim Care* 2008; **35**: 215-237

4 **Makras P**, Papapoulos SE. Medical treatment of hypercalcaemia. *Hormones* (*Athens*) 2009; **8**: 83-95

5 **Pellitteri PK**. Evaluation of hypercalcemia in relation to hyperparathyroidism. *Otolaryngol Clin North Am* 2010; **43**: 389-397

6 **Balasanthiran A**, Sandler B, Amonoo-Kuofi K, Swamy R, Kaniyur S, Kaplan F. Sarcoid granulomas in the parathyroid gland - a case of dual pathology: hypercalcaemia due to a parathyroid adenoma and coexistent sarcoidosis with granulomas located within the parathyroid adenoma and thyroid gland. *Endocr J* 2010; **57**: 603-607

7 **Fanari Z**, Kadikoy H, Haque W, Pacha O, Abdellatif A. Medical management of primary hyperparathyroidism with concomitant multiple myeloma. *Intern Med* 2010; **49**: 581-584

8 **Richey DS**, Welch BJ. Concurrent primary hyperparathyroidism and humoral hypercalcemia of malignancy in a patient with clear cell endometrial cancer. *South Med J* 2008; **101**: 1266-1268

9 **Giusti A**, Barone A, Pioli G, Girasole G, Razzano M, Pizzonia M, Pedrazzoni M, Palummeri E, Bianchi G. Heterogeneity in serum 25-hydroxy-vitamin D response to cholecalciferol in elderly women with secondary hyperparathyroidism and vitamin D deficiency. *J Am Geriatr Soc* 2010; **58**: 1489-1495

10 **Messa P**, Sindici C, Cannella G, Miotti V, Risaliti A, Gropuzzo M, Di Loreto PL, Bresadola F, Mioni G. Persistent secondary hyperparathyroidism after renal transplantation. *Kidney Int* 1998; **54**: 1704-1713

11 **Rude RK**, Oldham SB, Singer FR. Functional hypoparathyroidism and parathyroid hormone end-organ resistance in human magnesium deficiency. *Clin Endocrinol (Oxf)* 1976; **5**: 209-224

12 **Sahota O**, Mundey MK, San P, Godber IM, Hosking DJ. Vitamin D insufficiency and the blunted PTH response in established osteoporosis: the role of magnesium deficiency. *Osteoporos Int* 2006; **17**: 1013-1021

S- Editor Yang XC **L- Editor** Webster JR **E- Editor** Zhang DN

World Journal of Clinical Oncology

Online Submissions: http://www.wjgnet.com/2218-4333office
wjco@wjgnet.com
doi:10.5306/wjco.v3.i1.12

World J Clin Oncol 2012 January 10; 3(1): 12-14
ISSN 2218-4333 (online)

CASE REPORT

Optimal combination of radiofrequency ablation with chemoradiotherapy for locally advanced pancreatic cancer

Shinichi Ikuta, Ami Kurimoto, Hiroya Iida, Tsukasa Aihara, Makiko Takechi, Norihiko Kamikonya, Naoki Yamanaka

Shinichi Ikuta, Ami Kurimoto, Hiroya Iida, Tsukasa Aihara, Naoki Yamanaka, Department of Surgery, Meiwa General Hospital, Hyogo 663-8186, Japan
Makiko Takechi, Tsuchibashi Clinic, Kochi 780-0870, Japan
Norihiko Kamikonya, Department of Radiology, Hyogo College of Medicine, Hyogo 663-8501, Japan
Author contributions: Ikuta S and Takechi M wrote the paper; Kurimoto A, Iida H, Takechi M and Kamikonya N treated the patient; Aihara T and Yamanaka N contributed equally to the supportive work and supervision.
Correspondence to: Dr. Shinichi Ikuta, Department of Surgery, Meiwa General Hospital, Agenaruo 4-31, Nishinomiya, Hyogo 663-8186, Japan. ikuta@meiwa-hospital.com
Telephone: +81-798-471767 Fax: +81-798-477613
Received: September 8, 2011 Revised: October 25, 2011
Accepted: January 7, 2012
Published online: January 10, 2012

Key words: Chemotherapy; Locally advanced pancreatic cancer; Radiotherapy; Radiofrequency ablation

Peer reviewer: Thomas Yau, MBBS, MRCP, FHKCP, FHKAM, Department of Medicine, Queen Mary Hospital, University of Hong Kong, Room 405, 4/F Professorial Block, 102 Pokfulam Road, Hong Kong, China

Ikuta S, Kurimoto A, Iida H, Aihara T, Takechi M, Kamikonya N, Yamanaka N. Optimal combination of radiofrequency ablation with chemoradiotherapy for locally advanced pancreatic cancer. *World J Clin Oncol* 2012; 3(1): 12-14 Available from: URL: http://www.wjgnet.com/2218-4333/full/v3/i1/12.htm DOI: http://dx.doi.org/10.5306/wjco.v3.i1.12

Abstract

Problems have been reported in the treatment of pancreatic cancer with radiofrequency ablation (RFA), such as the friability of the organ itself. This report presents possible solutions to such problems. Although our patient suffered from locally advanced unresectable pancreatic cancer, she remained well at 18 mo after RFA with no evidence of recurrence. To ameliorate the side effects of RFA, after a palliative bypass procedure, the subject was treated with combined radiotherapy and chemotherapy. After this regimen had been administered, a contrast-enhanced computed tomography scan confirmed that RFA is a viable approach to the treatment of pancreatic cancer as the chemoradiotherapy had resulted in marked tumor shrinkage and pancreatic fibrosis; i.e., sufficient tumor ablation was achieved without serious RFA-related complications, such as pancreatitis or pancreatic fistulae. The present case suggests that RFA combined with preceding chemoradiotherapy is safe and effective for the palliative treatment of locally advanced pancreatic cancer.

INTRODUCTION

Radical surgery is the only potentially curative treatment for pancreatic cancer, but only 5%-25% of cases are indicated for resection due to its late presentation[1,2]. Most cases of pancreatic cancer are diagnosed at an advanced stage; i.e., when they display locally advanced (presence of perineural and vascular invasion) or metastatic disease (commonly in the liver, lungs and/or peritoneum). The prognosis of patients with unresectable pancreatic cancer is dismal. The median overall survival rate is 10-12 mo and 3-6 mo in patients with unresectable locally advanced cancer and metastatic disease, respectively[2]. In patients with locally advanced pancreatic cancer, chemotherapy with or without radiotherapy, has been applied to induce tumor regression, obtain local control, slow tumor growth and relieve pain and/or symptoms. However, the treatment options for locally advanced pancreatic cancer are limited, and new therapeutic measures are required.

Radiofrequency ablation (RFA) is a local thermal therapy that is widely used for the treatment of solid parenchymal tumors[1-3]. In particular, it is effective for treating liver tumors and has been successfully employed

in palliative therapy for tumors in the lung, kidney, brain, prostate and breast[1,2]. Although RFA appears to be an attractive treatment option for patients with unresectable, locally advanced and non-metastatic pancreatic cancer, the risk of thermal injury to the soft and friable pancreatic tissue has limited its clinical application. Indeed, a high frequency of life-threatening complications, such as necrotizing pancreatitis, has been reported after RFA for pancreatic tumors[4]. The aim of this report is to describe the case of a patient with locally advanced pancreatic cancer who was successfully treated with combination therapy involving open RFA and chemoradiotherapy, and thus, improve the safety and efficacy of RFA for pancreatic cancer.

CASE REPORT

A 60-year-old woman with diabetes mellitus presented with recent weight loss and a lack of appetite. A contrast-enhanced computed tomography (CE-CT) scan revealed a pancreatic head tumor measuring 35 mm in diameter (Figure 1A), which had infiltrated into the superior mesenteric vein (SMV). Endoscopic retrograde cholangiopancreatography demonstrated main pancreatic duct disruption in the head of the pancreas and distal common bile duct stricture. A diagnosis of pancreatic adenocarcinoma was confirmed by endoscopic ultrasound guided fine-needle aspiration cytology. She was then referred to our hospital for surgical treatment. Her laboratory findings showed mild liver dysfunction and elevated serum levels of carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9 (7.5 ng/mL, normal < 5; 759 U/mL, normal < 37, respectively).

During laparotomy, there was no evidence of liver metastasis or peritoneal involvement, but the tumor was found to be bigger than suggested by preoperative imaging. It had grown to a diameter of 40 mm and infiltrated into the distal SMV at the level of the jejunal branch, indicating locally advanced and unresectable disease. The patient consequently underwent common bile duct-jejunostomy and gastrojejunostomy. After the initial operation, we planned to treat the patient with chemoradiotherapy to reduce the size of the tumor and induce pancreatic fibrosis, followed by RFA if possible. Extra beam radiotherapy was started one month after the bypass surgery using a 10 MV X-ray at a total dose of 4500 cGy in 180 cGy fractions. The patient was then offered gemcitabine, which was administered intravenously at 1000 mg/m^2 on days 1, 8 and 15 followed by a 1-wk rest period. S-1 40 mg/m^2 was co-administered orally twice daily on days 1 to 14 of each cycle. The cycles were repeated every four weeks for four cycles. A second CE-CT scan taken after the completion of chemoradiotherapy confirmed that the pancreatic head mass had shrunk (to 20 mm in diameter) (Figure 1B). Her serum levels of CEA and CA19-9 decreased to 4.0 ng/mL and 120 U/mL, respectively. Since imaging studies revealed no evidence of distant metastases and the patient was in a good general condition, the patient elected to undergo operative RFA after providing informed consent.

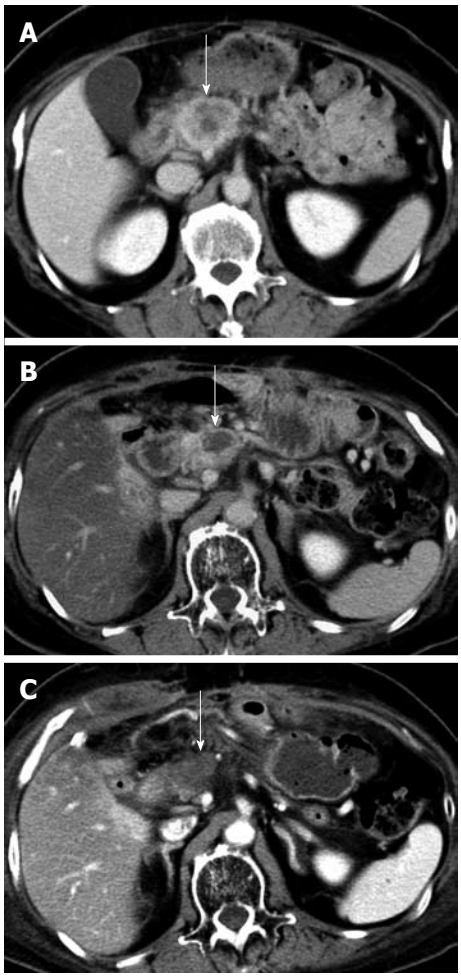

Figure 1 Abdominal contrast-enhanced computed tomography scan. A: contrast-enhanced computed tomography (CE-CT) scan showing a tumor in the pancreatic head before the first laparotomy (arrow); B: CE-CT scan taken after the chemoradiotherapy showing a reduction in the size of the tumor (arrow); C: CE-CT scan taken after the radiofrequency ablation showing a necrotic area that is suggestive of an ablated tumor (arrow).

During the second laparotomy, fibrotic changes, which had probably been induced by the chemoradiotherapy, were observed in the duodenal wall and pancreatic head, including the tumor and surrounding normal pancreatic tissue. Frozen section examination of a needle biopsy specimen detected a small number of viable malignant cells in the necrotic fibrous tissue. We decided to perform RFA as planned because radical resection with vascular reconstruction was considered impossible. We used the latest Cool-tip™ RFA system (Radionics Inc.) and a cooled electrode (17-gauge, 15 cm in length with 2 cm insertion for rapid tumor destruction). The radiofrequency needle was placed accurately into the tumor under ultrasonographic guidance. The coagulative effect of the treatment was monitored by intraoperative ultrasonography. Two overlapping ablations were performed, the first lasted for 4 min 30 s, and the second lasted for 3 min 30 s, resulting in an intratumoral temperature of 99 ℃. An abdominal drainage tube was left in place close to the ablated area.

After the procedure, the patient was intravenously

infused with octreotide acetate for 5 d to prevent pancreatitis. Consequently, the patient's postoperative course was uneventful; i.e., without complications such as pancreatitis, gastroduodenal bleeding, pancreatic fistulae and sepsis. A CE-CT scan obtained 8 d after the RFA showed a necrotic area in the head of the pancreas that corresponded to the ablation site (Figure 1C). One month after the RFA, her serum CEA and CA19-9 levels had returned to the normal range. The patient received postoperative chemotherapy with tegafur-uracil and is alive at 18 postoperative months with no signs of tumor recurrence.

DISCUSSION

The safety of RFA for pancreatic cancer is still under debate. In 2000, Matsui *et al*[3] first reported 20 patients with unresectable and metastatic pancreatic cancer who were treated with RFA. Of the 20 cases, two (10%) suffered critical complications; one patient died from septic shock, and the other from gastrointestinal bleeding. In 2004, Elias *et al*[4] reported their experience of two patients with multiple pancreatic renal cancer metastases who were treated with RFA. Unfortunately, both patients died from acute necrotizing pancreatitis and massive destruction of the normal pancreatic parenchyma. They concluded that because of the severe complications that it causes, RFA in the pancreas is not recommended. Recently, other authors have reported good postoperative results; i.e., no major procedure-related morbidity or mortality, after treating pancreatic cancer with RFA. To avoid damage to normal pancreatic tissue, Varshney *et al*[5] restricted the area of the tumor that was ablated in a study of three patients with unresectable pancreatic cancer. Moreover, Girelli *et al*[6] reported that reducing the RFA temperature from 105 ℃ to 90 ℃ resulted in a significant reduction in RFA-related complications. However, it is inevitable that such measures will attenuate the cytoreductive effect of RFA.

This case is the first to demonstrate the safety and efficacy of combining RFA with other palliative treatments such as chemoradiotherapy as a treatment for pancreatic cancer. We speculate that in the present case the chemoradiotherapy-induced peritumoral fibrosis reduced thermal conduction in the surrounding normal parenchyma, even at a higher ablation temperature than is recommended in the literature. Sufficient tumor ablation was thus achieved without increasing the risk of RFA-related pancreatitis or pancreatic fistulae. Moreover, RFA-related biliary injury and duodenal occlusion were avoided by biliary and gastric bypass surgery. Postoperative octreotide administration further reduced the risk of complications after RFA.

Although gemcitabine monotherapy is accepted as a standard first-line treatment for unresectable pancreatic cancer, gemcitabine and S-1 combination chemotherapy also has a favorable profile and results in a median overall survival of 9.3 mo[7]. Furthermore, several trials have demonstrated that the addition of radiation to chemotherapy is beneficial in terms of overall survival[8]. On the other hand, only a few studies have demonstrated a survival benefit of RFA for unresectable pancreatic cancer[9].

The application of RFA to the treatment of pancreatic tumors is still at an early stage and is undergoing research to improve its safety. The findings obtained in this case led us to the conclusion that RFA combined with preceding chemoradiotherapy is safe and might be more effective than using either modality alone, which could lead to better palliation of locally advanced pancreatic cancer. However, a case series study is required to confirm our encouraging results.

ACKNOWLEDGMENTS

This paper is dedicated to the memory of Dr. Chiaki Yasui who gave his life to the advancement of medical science.

REFERENCES

1 **Casadei R**, Ricci C, Pezzilli R, Serra C, Calculli L, Morselli-Labate AM, Santini D, Minni F. A prospective study on radiofrequency ablation locally advanced pancreatic cancer. *Hepatobiliary Pancreat Dis Int* 2010; **9**: 306-311

2 **Pezzilli R**, Serra C, Ricci C, Casadei R, Monari F, D'Ambra M, Minni F. Radiofrequency ablation for advanced ductal pancreatic carcinoma: is this approach beneficial for our patients? A systematic review. *Pancreas* 2011; **40**: 163-165

3 **Matsui Y**, Nakagawa A, Kamiyama Y, Yamamoto K, Kubo N, Nakase Y. Selective thermocoagulation of unresectable pancreatic cancers by using radiofrequency capacitive heating. *Pancreas* 2000; **20**: 14-20

4 **Elias D**, Baton O, Sideris L, Lasser P, Pocard M. Necrotizing pancreatitis after radiofrequency destruction of pancreatic tumours. *Eur J Surg Oncol* 2004; **30**: 85-87

5 **Varshney S**, Sewkani A, Sharma S, Kapoor S, Naik S, Sharma A, Patel K. Radiofrequency ablation of unresectable pancreatic carcinoma: feasibility, efficacy and safety. *JOP* 2006; **7**: 74-78

6 **Girelli R**, Frigerio I, Salvia R, Barbi E, Tinazzi Martini P, Bassi C. Feasibility and safety of radiofrequency ablation for locally advanced pancreatic cancer. *Br J Surg* 2010; **97**: 220-225

7 **Oh DY**, Cha Y, Choi IS, Yoon SY, Choi IK, Kim JH, Oh SC, Kim CD, Kim JS, Bang YJ, Kim YH. A multicenter phase II study of gemcitabine and S-1 combination chemotherapy in patients with unresectable pancreatic cancer. *Cancer Chemother Pharmacol* 2010; **65**: 527-536

8 **Loehrer PJ**, Powell ME, Cardenes HR, Wagner L, Brell JM, Ramanathan RK, Crane CH, Alberts SR, Benson AB III. A randomized phase III study of gemcitabine in combination with radiation therapy versus gemcitabine alone in patients with localized, unresectable pancreatic cancer: E4201. *J Clin Oncol* 2008; **26**: abstr 4506

9 **Zou YP**, Li WM, Zheng F, Li FC, Huang H, Du JD, Liu HR. Intraoperative radiofrequency ablation combined with 125 iodine seed implantation for unresectable pancreatic cancer. *World J Gastroenterol* 2010; **16**: 5104-5110

S- Editor Yang XC **L- Editor** Webster JR **E- Editor** Li JY

World Journal of Clinical Oncology

Online Submissions: http://www.wjgnet.com/2218-4333office
wjco@wjgnet.com
www.wjgnet.com

World J Clin Oncol 2012 January 10; 3(1): I
ISSN 2218-4333 (online)

Acknowledgments to reviewers of *World Journal of Clinical Oncology*

Many reviewers have contributed their expertise and time to the peer review, a critical process to ensure the quality of *World Journal of Clinical Oncology*. The editors and authors of the articles submitted to the journal are grateful to the following reviewers for evaluating the articles (including those published in this issue and those rejected for this issue) during the last editing time period.

Tim Van den Wyngaert, Dr., Antwerp University Hospital, Wilrijkstraat 10, 2650 Edegem, Belgium

Arianna L Kim, PhD, Herbert Irving Assistant Professor of Dermatology, Department of Dermatology, Columbia Medical Center, 1130 St. Nicholas Ave 321B, New York, NY 10032, United States; Shufeng Zhou, MD, PhD, A/Professor, School of Health Sciences, RMIT University, Bundoora, Victoria 3083, Australia

Thomas Yau, MBBS, MRCP, FHKCP, FHKAM, Department of Medicine, Queen Mary Hospital, University of Hong Kong, Room 405, 4/F Professorial Block, 102 Pokfulam Road, Hong Kong, China

WJCO World Journal of Clinical Oncology

Online Submissions: http://www.wjgnet.com/2218-4333office
wjco@wjgnet.com
www.wjgnet.com

World J Clin Oncol 2012 January 10; 3(1): I
ISSN 2218-4333 (online)

Events Calendar 2012

January 16-17, 2012
Biomarkers Summit Egypt
London, United Kingdom

January 25-26, 2012
Multi-Disciplinary Appoaches to Cancer Therapy
Dubai, United Arab Emirates

January 26-27, 2012
3rd National Conference: Renal and Bladder Cancer 2012
London, United Kingdom

January 30-31, 2012
2nd Annual Clinical Trials in Oncology
Rome, Italy

February 2-3, 2012
Stem Cells 2012 Conference and Exhibition
San Diego, United States

February 6-8, 2012
Mahidol International Conference on Infections and Cancers 2012
Bangkok, Thailand

February 12-17, 2012
Keystone Symposia: Cancer and Metabolism
Alberta, Canada

February 22-25, 2012
Excellence in Oncology
Istanbul, Turkey

March 8-10, 2012
10th International Congress on Targeted Anticancer Therapies
Amsterdam, Netherlands

March 9-10, 2012
13th European Congress: Perspectives in Lung Cancer
Amsterdam, Netherlands

March 14-16, 2012
BTOC-11 Biological Therapy of Cancer
Munich, Germany

March 15-17, 2012
3rd Conference on Therapeutic Resistance in Cancer
Quebec, Canada

March 29-30, 2012
Modern methods of diagnosis and treatment of malignant tumors
Kiev, Ukraine

April 13-15, 2012
Asian Oncology Summit 2012
Singapore, Singapore

April 20-21, 2012
Diagnosis and treatment of advanced forms of prostate cancer, bladder cancer and kidney cancer
Kiev, Ukraine

April 20-22, 2012
The 9th Meeting of Asian Society for Neuro-Oncology
Taipei, Taiwan

April 26-28, 2012
3rd International Video Workshop on Radical Surgery in Gynaecological Oncology
Prague, Czech Republic

April 28, 2012
Issues in Pediatric Oncology
Kiev, Ukraine

May 5-6, 2012
Radiation Research Methods as a diagnostic and therapeutic support in oncology
Kiev, Ukraine

May 17-18, 2012
Eurasian forum on the management of patients with tumors of the gastrointestinal tract
Uman, Ukraine

June 16-17, 2012
Issues of Neurosurgery, vascular neurosurgery, neurooncology, spinal surgery and spinal cord
Kiev, Ukraine

July 7-10, 2012
22nd Biennial Congress of the European Association for Cancer Research
Barcelona, Spain

July 21-28, 2012
Cancer In Women
Hawaii, HI, United States

July 25-27, 2012
5th Latin American Conference on Lung Cancer
Rio de Janeiro, Brazil

August 27-30, 2012
UICC World Cancer Congress 2012
Québec, Canada

September 6-8, 2012
The 8th International Jordanian Oncology Society Conference
Amman, Jordan

September 27-28, 2012
Current issues of diagnosis and treatment of oncogynecology diseases
IvanoFrankivsk, Ukraine

September 27-29, 2012
European Conference of Oncology Pharmacy
Budapest, Hungary

October 5-8, 2012
44th Congress of the International Society of Paediatric Oncology
London, United Kingdom

October 13-16, 2012
14th Biennial Meeting of the International Gynecologic Cancer Society
Vancouver, Canada

October 19, 2012
Modern aspects of diagnosis and treatment of breast cancer
Kiev, Ukraine

October 23-26, 2012
Sydney International Breast Cancer Congress 2012
Sydney, Australia

October 27-28, 2012
Optimization methods for radiation diagnosis in oncology

November 6-9, 2012
24th EORTC-NCI-AACR Symposium on "Molecular Targets and Cancer Therapeutics"
Dublin, Ireland

November 16-17, 2012
17th Annual Perspectives in Thoracic Oncology
New York, NY, United States

World Journal of Clinical Oncology

Online Submissions: http://www.wjgnet.com/2218-4333office
wjco@wjgnet.com
www.wjgnet.com

World J Clin Oncol 2012 January 10; 3(1): I-V
ISSN 2218-4333 (online)

GENERAL INFORMATION

World Journal of Clinical Oncology (*World J Clin Oncol*, *WJCO*, online ISSN 2218-4333, DOI: 10.5306) is a monthly peer-reviewed, online, open-access (OA), journal supported by an editorial board consisting of 316 experts in oncology from 33 countries.

The biggest advantage of the OA model is that it provides free, full-text articles in PDF and other formats for experts and the public without registration, which eliminates the obstacle that traditional journals possess and usually delays the speed of the propagation and communication of scientific research results. The open access model has been proven to be a true approach that may achieve the ultimate goal of the journals, i.e. the maximization of the value to the readers, authors and society.

Maximization of personal benefits

The role of academic journals is to exhibit the scientific levels of a country, a university, a center, a department, and even a scientist, and build an important bridge for communication between scientists and the public. As we all know, the significance of the publication of scientific articles lies not only in disseminating and communicating innovative scientific achievements and academic views, as well as promoting the application of scientific achievements, but also in formally recognizing the "priority" and "copyright" of innovative achievements published, as well as evaluating research performance and academic levels. So, to realize these desired attributes of *WJCO* and create a well-recognized journal, the following four types of personal benefits should be maximized. The maximization of personal benefits refers to the pursuit of the maximum personal benefits in a well-considered optimal manner without violation of the laws, ethical rules and the benefits of others. (1) Maximization of the benefits of editorial board members: The primary task of editorial board members is to give a peer review of an unpublished scientific article *via* online office system to evaluate its innovativeness, scientific and practical values and determine whether it should be published or not. During peer review, editorial board members can also obtain cutting-edge information in that field at first hand. As leaders in their field, they have priority to be invited to write articles and publish commentary articles. We will put peer reviewers' names and affiliations along with the article they reviewed in the journal to acknowledge their contribution; (2) Maximization of the benefits of authors: Since *WJCO* is an open-access journal, readers around the world can immediately download and read, free of charge, high-quality, peer-reviewed articles from *WJCO* official website, thereby realizing the goals and significance of the communication between authors and peers as well as public reading; (3) Maximization of the benefits of readers: Readers can read or use, free of charge, high-quality peer-reviewed articles without any limits, and cite the arguments, viewpoints, concepts, theories, methods, results, conclusion or facts and data of pertinent literature so as to validate the innovativeness, scientific and practical values of their own research achievements, thus ensuring that their articles have novel arguments or viewpoints, solid evidence and correct conclusion; and (4) Maximization of the benefits of employees: It is an iron law that a first-class journal is unable to exist without first-class editors, and only first-class editors can create a first-class academic journal. We insist on strengthening our team cultivation and construction so that every employee, in an open, fair and transparent environment, could contribute their wisdom to edit and publish high-quality articles, thereby realizing the maximization of the personal benefits of editorial board members, authors and readers, and yielding the greatest social and economic benefits.

Aims and scope

The aim of *WJCO* is to report rapidly new theories, methods and techniques for prevention, diagnosis, treatment, rehabilitation and nursing in the field of oncology. *WJCO* covers etiology, epidemiology, evidence-based medicine, informatics, diagnostic imaging, endoscopy, tumor recurrence and metastasis, tumor stem cells, radiotherapy, chemotherapy, interventional radiology, palliative therapy, clinical chemotherapy, biological therapy, minimally invasive therapy, physiotherapy, psycho-oncology, comprehensive therapy, oncology-related traditional medicine, integrated Chinese and Western medicine, and nursing. *WJCO* covers tumors in various organs/tissues, including the female reproductive system, bone and soft tissue, respiratory system, urinary system, endocrine system, skin, breast, nervous system, head and neck, digestive system, and hematologic and lymphatic system. The journal also publishes original articles and reviews that report the results of applied and basic research in fields related to oncology, such as immunology, physiopathology, cell biology, pharmacology, medical genetics, and pharmacology of Chinese herbs.

Columns

The columns in the issues of *WJCO* will include: (1) Editorial: To introduce and comment on major advances and developments in the field; (2) Frontier: To review representative achievements, comment on the state of current research, and propose directions for future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Basic Research: To provide Guidelines for basic research; (6) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (7) Review: To review systemically progress and unresolved problems in the field, comment on the state of current research, and make suggestions for future work; (8) Original Articles: To report innovative and original findings in oncology; (9) Brief Articles: To briefly report the novel and innovative findings in oncology; (10) Case Report: To report a rare or typical case; (11) Letters to the Editor: To discuss and make reply to the contributions published in *WJCO*, or to introduce and comment on a controversial issue of general interest; (12) Book Reviews: To introduce and comment on quality monographs of oncology; and (13) Guidelines: To introduce consensuses and guidelines reached by international and national academic authorities worldwide on the research oncology.

Name of journal

World Journal of Clinical Oncology

ISSN

ISSN 2218-4333 (online)

Editor-in-chief

Stuart K Calderwood, PhD, Associate Professor, Director Molecular and Cellular Radiation Oncology, Department of Radiation Oncology, Beth Israel Deaconess Medical Center,

Harvard Medical School, 99 Brookline Avenue, Boston, MA 02215, United States

Editorial Office
World Journal of Clinical Oncology
Editorial Department: Room 903, Building D,
Ocean International Center,
No. 62 Dongsihuan Zhonglu,
Chaoyang District, Beijing 100025, China
E-mail: wjco@wjgnet.com
http://www.wjgnet.com
Telephone: +86-10-85381892
Fax: +86-10-85381893

Indexed and Abstracted in
PubMed Central, PubMed, Digital Object Identifer, and Directory of Open Access Journals.

Published by
Baishideng Publishing Group Co., Limited

SPECIAL STATEMENT

All articles published in this journal represent the viewpoints of the authors except where indicated otherwise.

Biostatistical editing
Statisital review is performed after peer review. We invite an expert in Biomedical Statistics from to evaluate the statistical method used in the paper, including *t*-test (group or paired comparisons), chi-squared test, Ridit, probit, logit, regression (linear, curvilinear, or stepwise), correlation, analysis of variance, analysis of covariance, *etc*. The reviewing points include: (1) Statistical methods should be described when they are used to verify the results; (2) Whether the statistical techniques are suitable or correct; (3) Only homogeneous data can be averaged. Standard deviations are preferred to standard errors. Give the number of observations and subjects (*n*). Losses in observations, such as drop-outs from the study should be reported; (4) Values such as ED50, LD50, IC50 should have their 95% confidence limits calculated and compared by weighted probit analysis (Bliss and Finney); and (5) The word 'significantly' should be replaced by its synonyms (if it indicates extent) or the *P* value (if it indicates statistical significance).

Conflict-of-interest statement
In the interests of transparency and to help reviewers assess any potential bias, *WJCO* requires authors of all papers to declare any competing commercial, personal, political, intellectual, or religious interests in relation to the submitted work. Referees are also asked to indicate any potential conflict they might have reviewing a particular paper. Before submitting, authors are suggested to read "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Ethical Considerations in the Conduct and Reporting of Research: Conflicts of Interest" from International Committee of Medical Journal Editors (ICMJE), which is available at: http://www.icmje.org/ethical_4conflicts.html.

Sample wording: [Name of individual] has received fees for serving as a speaker, a consultant and an advisory board member for [names of organizations], and has received research funding from [names of organization]. [Name of individual] is an employee of [name of organization]. [Name of individual] owns stocks and shares in [name of organization]. [Name of individual] owns patent [patent identification and brief description].

Statement of informed consent
Manuscripts should contain a statement to the effect that all human studies have been reviewed by the appropriate ethics committee or it should be stated clearly in the text that all persons gave their informed consent prior to their inclusion in the study. Details that might disclose the identity of the subjects under study should be omitted. Authors should also draw attention to the Code of Ethics of the World Medical Association (Declaration of Helsinki, 1964, as revised in 2004).

Statement of human and animal rights
When reporting the results from experiments, authors should follow the highest standards and the trial should conform to Good Clinical Practice (for example, US Food and Drug Administration Good Clinical Practice in FDA-Regulated Clinical Trials; UK Medicines Research Council Guidelines for Good Clinical Practice in Clinical Trials) and/or the World Medical Association Declaration of Helsinki. Generally, we suggest authors follow the lead investigator's national standard. If doubt exists whether the research was conducted in accordance with the above standards, the authors must explain the rationale for their approach and demonstrate that the institutional review body explicitly approved the doubtful aspects of the study.

Before submitting, authors should make their study approved by the relevant research ethics committee or institutional review board. If human participants were involved, manuscripts must be accompanied by a statement that the experiments were undertaken with the understanding and appropriate informed consent of each. Any personal item or information will not be published without explicit consents from the involved patients. If experimental animals were used, the materials and methods (experimental procedures) section must clearly indicate that appropriate measures were taken to minimize pain or discomfort, and details of animal care should be provided.

SUBMISSION OF MANUSCRIPTS

Manuscripts should be typed in 1.5 line spacing and 12 pt. Book Antiqua with ample margins. Number all pages consecutively, and start each of the following sections on a new page: Title Page, Abstract, Introduction, Materials and Methods, Results, Discussion, Acknowledgements, References, Tables, Figures, and Figure Legends. Neither the editors nor the publisher are responsible for the opinions expressed by contributors. Manuscripts formally accepted for publication become the permanent property of Baishideng Publishing Group Co., Limited, and may not be reproduced by any means, in whole or in part, without the written permission of both the authors and the publisher. We reserve the right to copy-edit and put onto our website accepted manuscripts. Authors should follow the relevant guidelines for the care and use of laboratory animals of their institution or national animal welfare committee. For the sake of transparency in regard to the performance and reporting of clinical trials, we endorse the policy of the ICMJE to refuse to publish papers on clinical trial results if the trial was not recorded in a publicly-accessible registry at its outset. The only register now available, to our knowledge, is http://www.clinicaltrials.gov sponsored by the United States National Library of Medicine and we encourage all potential contributors to register with it. However, in the case that other registers become available you will be duly notified. A letter of recommendation from each author's organization should be provided with the contributed article to ensure the privacy and secrecy of research is protected.

Authors should retain one copy of the text, tables, photographs and illustrations because rejected manuscripts will not be returned to the author(s) and the editors will not be responsible for loss or damage to photographs and illustrations sustained during mailing.

Online submissions
Manuscripts should be submitted through the Online Submission System at: http://www.wjgnet.com/2218-4333office. Authors are highly recommended to consult the ONLINE INSTRUCTIONS TO AUTHORS (http://www.wjgnet.com/2218-4333/g_info_20100722172206.htm) before attempting to submit online. For assistance, authors encountering problems with the Online Submission System may send an email describing the problem to wjco@wjgnet.com, or by telephone: +86-10-85381892. If you submit your manuscript online, do not make a postal contribution. Repeated online submission for the same manuscript is strictly prohibited.

MANUSCRIPT PREPARATION

All contributions should be written in English. All articles must be submitted using word-processing software. All submissions must be

typed in 1.5 line spacing and 12 pt. Book Antiqua with ample margins. Style should conform to our house format. Required information for each of the manuscript sections is as follows:

Title page

Title: Title should be less than 12 words.

Running title: A short running title of less than 6 words should be provided.

Authorship: Authorship credit should be in accordance with the standard proposed by International Committee of Medical Journal Editors, based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.

Institution: Author names should be given first, then the complete name of institution, city, province and postcode. For example, Xu-Chen Zhang, Li-Xin Mei, Department of Pathology, Chengde Medical College, Chengde 067000, Hebei Province, China. One author may be represented from two institutions, for example, George Sgourakis, Department of General, Visceral, and Transplantation Surgery, Essen 45122, Germany; George Sgourakis, 2nd Surgical Department, Korgialenio-Benakio Red Cross Hospital, Athens 15451, Greece

Author contributions: The format of this section should be: Author contributions: Wang CL and Liang L contributed equally to this work; Wang CL, Liang L, Fu JF, Zou CC, Hong F and Wu XM designed the research; Wang CL, Zou CC, Hong F and Wu XM performed the research; Xue JZ and Lu JR contributed new reagents/analytic tools; Wang CL, Liang L and Fu JF analyzed the data; and Wang CL, Liang L and Fu JF wrote the paper.

Supportive foundations: The complete name and number of supportive foundations should be provided, e.g. Supported by National Natural Science Foundation of China, No. 30224801

Correspondence to: Only one corresponding address should be provided. Author names should be given first, then author title, affiliation, the complete name of institution, city, postcode, province, country, and email. All the letters in the email should be in lower case. A space interval should be inserted between country name and email address. For example, Montgomery Bissell, MD, Professor of Medicine, Chief, Liver Center, Gastroenterology Division, University of California, Box 0538, San Francisco, CA 94143, United States. montgomery.bissell@ucsf.edu

Telephone and fax: Telephone and fax should consist of +, country number, district number and telephone or fax number, e.g. Telephone: +86-10-59080039 Fax: +86-10-85381893

Peer reviewers: All articles received are subject to peer review. Normally, three experts are invited for each article. Decision for acceptance is made only when at least two experts recommend an article for publication. Reviewers for accepted manuscripts are acknowledged in each manuscript, and reviewers of articles which were not accepted will be acknowledged at the end of each issue. To ensure the quality of the articles published in *WJCO*, reviewers of accepted manuscripts will be announced by publishing the name, title/position and institution of the reviewer in the footnote accompanying the printed article. For example, reviewers: Professor Jing-Yuan Fang, Shanghai Institute of Digestive Disease, Shanghai, Affiliated Renji Hospital, Medical Faculty, Shanghai Jiaotong University, Shanghai, China; Professor Xin-Wei Han, Department of Radiology, The First Affiliated Hospital, Zhengzhou University, Zhengzhou, Henan Province, China; and Professor Anren Kuang, Department of Nuclear Medicine, Huaxi Hospital, Sichuan University, Chengdu, Sichuan Province, China.

Abstract

There are unstructured abstracts (no less than 256 words) and structured abstracts (no less than 480). The specific requirements for structured abstracts are as follows:

An informative, structured abstracts of no less than 480 words should accompany each manuscript. Abstracts for original contributions should be structured into the following sections. AIM (no more than 20 words): Only the purpose should be included. Please write the aim as the form of "To investigate/study/…; MATERIALS AND METHODS (no less than 140 words); RESULTS (no less than 294 words): You should present *P* values where appropriate and must provide relevant data to illustrate how they were obtained, e.g. 6.92 ± 3.86 *vs* 3.61 ± 1.67, $P < 0.001$; CONCLUSION (no more than 26 words).

Key words

Please list 5-10 key words, selected mainly from *Index Medicus*, which reflect the content of the study.

Text

For articles of these sections, original articles and brief articles, the main text should be structured into the following sections: INTRODUCTION, MATERIALS AND METHODS, RESULTS and DISCUSSION, and should include appropriate Figures and Tables. Data should be presented in the main text or in Figures and Tables, but not in both. The main text format of these sections, editorial, topic highlight, case report, letters to the editors, can be found at: http://www.wjgnet.com/2218-4333/g_info_list.htm.

Illustrations

Figures should be numbered as 1, 2, 3, *etc*., and mentioned clearly in the main text. Provide a brief title for each figure on a separate page. Detailed legends should not be provided under the figures. This part should be added into the text where the figures are applicable. Figures should be either Photoshop or Illustrator files (in tiff, eps, jpeg formats) at high-resolution. Examples can be found at: http://www.wjgnet.com/1007-9327/13/4520.pdf; http://www.wjgnet.com/1007-9327/13/4554.pdf; http://www.wjgnet.com/1007-9327/13/4891.pdf; http://www.wjgnet.com/1007-9327/13/4986.pdf; http://www.wjgnet.com/1007-9327/13/4498.pdf. Keeping all elements compiled is necessary in line-art image. Scale bars should be used rather than magnification factors, with the length of the bar defined in the legend rather than on the bar itself. File names should identify the figure and panel. Avoid layering type directly over shaded or textured areas. Please use uniform legends for the same subjects. For example: Figure 1 Pathological changes in atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: …*etc*. It is our principle to publish high resolution-figures for the printed and E-versions.

Tables

Three-line tables should be numbered 1, 2, 3, *etc*., and mentioned clearly in the main text. Provide a brief title for each table. Detailed legends should not be included under tables, but rather added into the text where applicable. The information should complement, but not duplicate the text. Use one horizontal line under the title, a second under column heads, and a third below the Table, above any footnotes. Vertical and italic lines should be omitted.

Notes in tables and illustrations

Data that are not statistically significant should not be noted. $^{a}P < 0.05$, $^{b}P < 0.01$ should be noted ($P > 0.05$ should not be noted). If there are other series of *P* values, $^{c}P < 0.05$ and $^{d}P < 0.01$ are used. A third series of *P* values can be expressed as $^{e}P < 0.05$ and $^{f}P < 0.01$. Other notes in tables or under illustrations should be expressed as ^{1}F, ^{2}F, ^{3}F; or sometimes as other symbols with a superscript (Arabic numerals) in the upper left corner. In a multi-curve illustration, each curve should be labeled with ●, ○, ■, □, ▲, △, *etc*., in a certain sequence.

Acknowledgments

Brief acknowledgments of persons who have made genuine contributions to the manuscript and who endorse the data and conclusions should be included. Authors are responsible for obtaining written permission to use any copyrighted text and/or illustrations.

REFERENCES

Coding system

The author should number the references in Arabic numerals according to the citation order in the text. Put reference numbers in square brackets in superscript at the end of citation content or after the cited author's name. For citation content which is part of the narration, the coding number and square brackets should be typeset normally. For example, "Crohn's disease (CD) is associated with increased intestinal permeability[1,2]". If references are cited directly in the text, they should be put together within the text, for example, "From references[19,22-24], we know that..."

When the authors write the references, please ensure that the order in text is the same as in the references section, and also ensure the spelling accuracy of the first author's name. Do not list the same citation twice.

PMID and DOI

Pleased provide PubMed citation numbers to the reference list, e.g. PMID and DOI, which can be found at http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed and http://www.crossref.org/SimpleTextQuery/, respectively. The numbers will be used in E-version of this journal.

Style for journal references

Authors: the name of the first author should be typed in bold-faced letters. The family name of all authors should be typed with the initial letter capitalized, followed by their abbreviated first and middle initials. (For example, Lian-Sheng Ma is abbreviated as Ma LS, Bo-Rong Pan as Pan BR). The title of the cited article and italicized journal title (journal title should be in its abbreviated form as shown in PubMed), publication date, volume number (in black), start page, and end page [PMID: 11819634 DOI: 10.3748/wjg.13.5396].

Style for book references

Authors: the name of the first author should be typed in bold-faced letters. The surname of all authors should be typed with the initial letter capitalized, followed by their abbreviated middle and first initials. (For example, Lian-Sheng Ma is abbreviated as Ma LS, Bo-Rong Pan as Pan BR) Book title. Publication number. Publication place: Publication press, Year: start page and end page.

Format

Journals

English journal article (list all authors and include the PMID where applicable)

1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

Chinese journal article (list all authors and include the PMID where applicable)

2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

The format for how to accurately write common units and quantums can be found at: http://www.wjgnet.com/2218-4333/g_info_20100723153305.htm.

Abbreviations

Standard abbreviations should be defined in the abstract and on first mention in the text. In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Permissible abbreviations are listed in Units, Symbols and Abbreviations: A Guide for Biological and Medical Editors and Authors (Ed. Baron DN, 1988) published by The Royal Society of Medicine, London. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, mAb, can be used directly without further explanation.

Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
Genotypes: *gyrA*, *arg* 1, *c myc*, *c fos*, *etc.*
Restriction enzymes: *Eco*RI, *Hin*dI, *Bam*HI, *Kbo* I, *Kpn* I, *etc.*
Biology: *H. pylori*, *E coli*, *etc.*

Examples for paper writing

Editorial: http://www.wjgnet.com/2218-4333/g_info_20100723140942.htm

Frontier: http://www.wjgnet.com/2218-4333/g_info_20100723141035.htm

Topic highlight: http://www.wjgnet.com/2218-4333/g_info_20100723141239.htm

Observation: http://www.wjgnet.com/2218-4333/g_info_20100723141532.htm

Guidelines for basic research: http://www.wjgnet.com/2218-4333/g_info_20100723142040.htm

Guidelines for clinical practice: http://www.wjgnet.com/2218-5836/g_info_20100723142248.htm

Review: http://www.wjgnet.com/2218-4333/g_info_20100723145519.htm

Original articles: http://www.wjgnet.com/2218-4333/g_info_20100723145856.htm

Brief articles: http://www.wjgnet.com/2218-4333/g_info_20100723150253.htm

Case report: http://www.wjgnet.com/2218-4333/g_info_20100723150420.htm

Letters to the editor: http://www.wjgnet.com/2218-4333/g_info_20100723150642.htm

Book reviews: http://www.wjgnet.com/2218-4333/g_info_20100723150839.htm

Guidelines: http://www.wjgnet.com/2218-4333/g_info_20100723150924.htm

SUBMISSION OF THE REVISED MANUSCRIPTS AFTER ACCEPTED

Please revise your article according to the revision policies of *WJCO*. The revised version including manuscript and high-resolution image figures (if any) should be re-submitted online (http://www.wjgnet.com/2218-4333office/). The author should send the copyright transfer letter, responses to the reviewers, English language Grade B certificate (for non-native speakers of English) and final manuscript checklist to wjco@wjgnet.com.

Language evaluation

The language of a manuscript will be graded before it is sent for revision. (1) Grade A: priority publishing; (2) Grade B: minor language polishing; (3) Grade C: a great deal of language polishing needed; and (4) Grade D: rejected. Revised articles should reach Grade A or B.

Copyright assignment form

Please download a Copyright assignment form from http://www.wjgnet.com/2218-4333/g_info_20100723153117.htm.

Responses to reviewers

Please revise your article according to the comments/suggestions provided by the reviewers. The format for responses to the reviewers' comments can be found at: http://www.wjgnet.com/2218-4333/g_info_20100723152755.htm.

Proof of financial support

For paper supported by a foundation, authors should provide a copy of the document and serial number of the foundation.

Links to documents related to the manuscript

WJCO will be initiating a platform to promote dynamic interactions between the editors, peer reviewers, readers and authors. After a manuscript is published online, links to the PDF version of the submitted manuscript, the peer-reviewers' report and the revised manuscript will be put on-line. Readers can make comments on the peer reviewer's report, authors' responses to peer reviewers, and the revised manuscript. We hope that authors will benefit from this feedback and be able to revise the manuscript accordingly in a timely manner.

Science news releases

Authors of accepted manuscripts are suggested to write a science news item to promote their articles. The news will be released rapidly at EurekAlert/AAAS (http://www.eurekalert.org). The title for news items should be less than 90 characters; the summary should be less than 75 words; and main body less than 500 words. Science news items should be lawful, ethical, and strictly based on your original content with an attractive title and interesting pictures.

Publication fee

WJCO is an international, peer-reviewed, Open-Access, online journal. Articles published by this journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license. Authors of accepted articles must pay a publication fee. The related standards are as follows. Publication fee: 1300 USD per article. Editorial, topic highlights, original articles, brief articles, book reviews and letters to the editor are published free of charge.