Safety and Anti-tumor Effects of Docetaxel Plus Cisplatin in Intermediate- and High-risk Endometrial Cancer

DAISUKE MIYAHARA, TAKAHIRO KATSUTA, MIYAKO MAEHARA, YOKO TAKAHASHI, SATOSHI FUKAGAWA, KOUHEI MIYATA, CHIHIRO KIYOSHIMA, FUSANORI YOTSUMOTO, HARUCHIKA ANAN and SHINGO MIYAMOTO

Department of Obstetrics and Gynecology, Faculty of Medicine, Fukuoka University, Fukuoka, Japan

Reprinted from
ANTICANCER RESEARCH 36: 3725-3730 (2016)
Abstract. Background: Endometrial cancer (EC) has a poor prognosis due to drug resistance. Patients and Methods: We evaluated the safety and efficacy of adjuvant combination chemotherapy with docetaxel plus cisplatin ((DP) docetaxel, 70 mg/m²; cisplatin, 60 mg/m²; every 28 days) in EC patients at intermediate-risk (IR) or high-risk (HR) for recurrence. Results: Sixty-four patients diagnosed with EC were enrolled. Stage-I, -II, -III and -IV disease was noted in 23, 7, 28 and 6 patients, respectively. Histopathological analyses revealed that 56, 3, 1 and 4 patients had endometrioid, serous, clear-cell or “other” types of carcinoma. Grade-3/4 hematologic toxicities were found at 80% and 95% in patients in IR and HR groups, respectively. In IR and HR groups, mean progression-free (PFS) survival was 69.5 and 29.5, while overall survival (OS) was 59.6 and 47.5 months, respectively. Conclusion: DP may be clinically safe and useful treatment for EC.

In 2013, the number of patients with newly diagnosed endometrial cancer (EC) was 49,560 and the annual number of deaths due to EC was 8,190 (1). The annual report of the International Federation of Gynecology and Obstetrics (FIGO) in 2013 revealed that (based on the FIGO classification from 1988) 26,531, 973, 1048 and 255 patients had Stage-I, -II, -III and -IV EC and that overall survival (OS) at 5 years was 90%, 78%, 62% and 21%, respectively (2). Accordingly, advanced EC has been recognized as carrying a poor prognosis.

Histology reveals that EC comprises four types: “endometrioid”, “serous”, “clear-cell carcinoma” and “other”. The prognosis of endometrial cancer is dependent upon histological subtypes and clinical characteristics (clinical stage, metastatic lesions). Risk of recurrence is divided into three categories (low, intermediate, high) according to these prognostic factors (3); EC treatment is initiated according to these three categories.

Primary treatment of EC is surgery: a hysterectomy and bilateral salpingo-oophorectomy with/without dissection of pelvic and para-aortic lymph nodes. Postoperatively, patients are treated with chemotherapy regimens (platinum-containing compounds, taxanes) dependent upon recurrence risk (4). However, whether cisplatin or carboplatin and paclitaxel or docetaxel should be combined is not known.

To ascertain the safety and efficacy of anticancer agents in patients with intermediate-risk (IR) or high-risk (HR) EC, we undertook adjuvant chemotherapy with docetaxel and cisplatin (DP).

Patients and Methods

Patients. This retrospective investigation assessed 184 patients with newly-diagnosed EC between 2005 and 2012. Patients underwent peritoneal washing, a total hysterectomy, radical hysterectomy, bilateral salpingo-oophorectomy or pelvic lymphadenectomy and dissection of para-aortic lymph nodes for EC. We reclassified 184 patients according to guidelines for EC set by the FIGO in 2008. Risk of EC recurrence was based on 2013 guidelines set by the Japan Society of Gynecologic Oncology (JSGO). Patients with uterine sarcoma were excluded from our study.

Criteria for inclusion into groups. Criteria for inclusion into the IR group were: (i) endometrioid adenocarcinoma G1 or G2 and ≥50% myometrial invasion; (ii) endometrioid adenocarcinoma G3 and ≤50% myometrial invasion; (iii) serous adenocarcinoma or clear-cell adenocarcinoma and no myometrial invasion; (iv) no cervical invasion; (v) venous or lymphatic invasion; (vi) no distant metastasis.

Criteria for inclusion into the HR group were: (i) endometrioid adenocarcinoma G3 and ≥50% myometrial invasion; (ii) serous adenocarcinoma or clear-cell adenocarcinoma and no myometrial invasion; (iii) spread to uterine adnexae, serosa or the cardinal ligament; (iv) cervical invasion; (v) invasion of the vaginal wall; (vi) metastasis into pelvic or para-aortic lymph nodes; (vii) vesical or rectal invasion; (viii) peritoneal dissemination; (ix) distant metastasis.
Treatment schedule. Patients received DP (docetaxel, 70 mg/m²; cisplatin, 60 mg/m²) every 28 days. Treatment was continued until disease progression or treatment completion. Treatment in the IR group was three cycles and six cycles in the HR group. Study treatment was delayed if any of the following were encountered on the scheduled day of administration or previous day: neutrophil count <1,500/mm³; platelet count <75,000/mm³; aspartate aminotransferase >100 IU/l; alanine aminotransferase >100 IU/l; total bilirubin >1.5 mg/dl; serum creatinine >1.50 mg/dl; grade-3 or grade-4 peripheral neuropathy; proteinuria grade ≥2; hemorrhage; stomatitis; fatigue and/or diarrhea.

Evaluation of efficacy and safety. Primary endpoint was prevalence of completion of scheduled chemotherapy, progression-free survival (PFS) and OS. Secondary endpoints were grade 3/4 toxicity and treatment response. Toxicity was assessed according to the Common Toxicity Criteria of the National Cancer Institute v4.0 (Japanese version issued by the Japan Clinical Oncology Group).

Results

Patients' characteristics. Twenty patients were placed in the IR group and 44 in the HR group according to the risk factors for EC recurrence. Patients' characteristics are shown in Table I. Median age of the IR group was 58 (range=42-73) years and that of the HR group was 58 (range=34-78) years. All patients had an Eastern Cooperative Oncology Group performance status of zero.

In the IR group, all patients had Stage-I disease (FIGO classification 2008). In this group, according to histopathologic analyses, 4 patients had endometrioid adenocarcinoma grade 1 (Stage-IB disease), 9 patients had endometrioid adenocarcinoma grade 2 (Stage-IB disease) and 7 patients had endometrioid adenocarcinoma grade 3 (Stage-IA disease).

In the HR group, according to FIGO 2008, 3 patients had Stage-I disease, 7 patients had Stage-II disease, 28 patients had Stage-III disease and 6 patients had Stage-IV disease. In this group, according to histopathological analyses, 36 had endometrial carcinoma, 3 had serous or mucinous adenocarcinoma, 1 patient had clear-cell adenocarcinoma and 2 patients had “other” type of adenocarcinoma.

Adverse events. Table II shows the prevalence and types of adverse events. Hematologic toxic events were the main major severe adverse events in both groups. In IR and HR groups, grade 3/4 hematologic toxicities (including neutropenia) were found in 80% and 95% of subjects, respectively. Grade-3 diarrhea occurred in 2 patients (10%) in the IR group and in 2 patients (5%) in the HR group. Neuropathy or nephropathy was not observed in either group.

Treatment completion. All patients in the IR group completed DP treatment. Among the 44 patients in the HR group who received DP treatment, 39 (89%) completed the treatment. Treatment was discontinued in 5 patients at the patient's discretion (1 case) and because new lesions developed (4 cases) during DP treatment.

Response. PFS and OS were estimated using the Kaplan–Meier method (Figure 1A and B). In the IR and HR groups, mean PFS was 69.5 and 29.5 (log rank test, \( p=0.00312 \)), whereas mean OS was 59.6 and 47.5 months (log rank test, \( p=0.00527 \)), respectively.

One patient in the IR group had EC recurrence. She had metastasis in pelvic lymph nodes 13 months after the final course of DP. In her recurrent lesion, cancer cells (which were undifferentiated and produced granulocyte colony-stimulating factor) transformed into an extremely malignant phenotype.

No recurrence was found in the 3 patients with Stage-I disease in the HR group. In the HR group, 4 patients had EC recurrence during DP treatment. One patient with Stage-IIIa disease and grade-1 endometrioid adenocarcinoma discontinued treatment of her own volition; she had no new lesions at 65 months. The remaining 4 patients had EC recurrence during DP treatment. One patient (case number 1; clinical Stage-IIIA and grade-3 endometrioid adenocarcinoma) had new lesions in the peritoneal cavity and lungs after the third course of chemotherapy. One patient (case number 2; clinical Stage IIIC1 and grade-3 endometrioid adenocarcinoma) had new lesions in the peritoneal cavity after the fifth course of chemotherapy. The third case (clinical Stage IIIC2 and grade-1 endometrioid adenocarcinoma with partial grade-3 endometrioid adenocarcinoma) had a metastatic lesion in para-aortic lymph nodes after the third course of chemotherapy.
chemotherapy. The fourth patient (clinical Stage IIIC2 and grade-3 endometrioid adenocarcinoma) suffered recurrence with peritoneal carcinomatosis and died soon afterwards due to intestinal obstruction. In 3 patients with serous-type carcinomas, 1 patient with clear-cell carcinoma and 5 cases with other types of carcinoma, no recurrence was found even at the advanced stage.

**Discussion**

We investigated the efficacy and safety of DP treatment in EC patients according to the risk factors for EC recurrence set by the JSGO. Prevalence of completion of DP treatment in IR and HR groups was high. Neutropenia was the main severe adverse event (excluding fever or infectious events) in both groups. Prevalence of recurrence was 1 in 20 patients (5%) in the IR group and 4 in 44 patients (9%) in the HR group. Two large studies have focused on differences in the efficacy of chemotherapy between doxorubicin and cisplatin (AP) and doxorubicin (A) alone (5, 6). Those studies reported that the response to AP was increased significantly compared with that of A without, however, any significant difference in survival found between AP and A.

In the GOG 177 study, a combination of paclitaxel, doxorubicin and cisplatin (TAP) was compared with that of AP as adjuvant chemotherapy in 287 patients with advanced EC or recurrent EC (7). Response, OS and PFS in patients treated with TAP were improved significantly compared with those treated with AP. Thirty-nine percent of patients treated with TAP had grade-2/3 peripheral neurotoxicity, compared

---

**Table II. Adverse events.**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Intermediate-risk (n=20)</th>
<th>High-risk (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Aminotransferase increase</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Ileus</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Stomach pain</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
with 5% of patients who received AP. Treatment with TAP and AP was tolerated with regard to hematologic adverse events.

Sovak et al. reported on the efficacy of adjuvant chemotherapy using paclitaxel and carboplatin (TC) in patients who had optimal cytoreduction of Stage-III and -IV EC (8). TC treatment was well-tolerated and 3-year disease-specific survival in these patients was 56%. However, treatment was very heterogeneous: 21% of patients received external-beam radiation, 10% had vaginal brachytherapy, while the remainder underwent individualized treatment.

In a small retrospective study, Hidaka et al. compared patients receiving cisplatin, doxorubicin and cyclophosphamide (CAP) with those receiving TC (9). Three-year PFS and OS was 50% and 75%, respectively, in the TC group, and 38% and 50%, respectively, in the CAP group. Patients receiving TC suffered fewer toxic effects than those receiving CAP.

In the present study, DP treatment did not induce neurotoxicity or nephrotoxicity and treatment due to adverse events was not interrupted. Nevertheless, the prevalence of neutropenia was very high. Our study cohort was heterogeneous but the prognosis seemed to be favorable. A randomized study comparing treatment of AP, DP or TC for patients with advanced or recurrent EC (JGOG2043) is in progress and should provide sufficient information for EC treatment.

During the past 30 years, EC has been classified broadly into two subtypes on the basis of histologic characteristics, expression of hormone receptors and histologic grade (10). This dual classification started to become incorporated into clinical decision-making algorithms to stratify high-risk patients; however, its prognostic value is limited because ≈20% of patients with grade-I (type-I) endometrioid adenocarcinoma relapse and ≈50% of patients with non-endometrioid (type-II) EC do not suffer recurrence (10). In addition, how 15%-20% of patients with high-grade endometrioid adenocarcinoma should be divided in this dual model is not clear (11, 12).

In the present study, 1 patient with intermediate risk for recurrence (clinical Stage IB and grade-1 endometrioid adenocarcinoma) relapsed with an extremely malignant phenotype at a distant metastatic lesion. In addition, 4 patients with grade-3 endometrioid adenocarcinoma suffered recurrence, whereas patients with specific histologic subtypes did not suffer recurrence.

Recently, it has become increasingly clear that EC comprises of a range of diseases with distinct genetic and molecular features (12-15). Development of a novel therapeutic agent for various subtypes would improve clinical outcome.

Conclusion

Our results suggest that DP is a therapeutically safe and useful regimen. Data from the present study could aid in development of novel molecular-targeted agents for EC treatment.

Conflicts of Interest

No potential conflicts of interest are disclosed.

Funding

This work was supported in part by a Grant-in-Aid for Scientific Research (B) (No. 26293362), a Grant-in-Aid for Challenging Exploratory Research (No. 26670731), the Center for Advanced Molecular Medicine, Fukuoka University from the Ministry of Education, Culture, Sports, Science and Technology (Tokyo, Japan) and a Grant-in-Aid from the Kakihara Science and Technology Foundation (Fukuoka, Japan) to S. Miyamoto.

References

10 Bokhman JV: Two pathogenetic types of endometrial carcinoma. Gynecol Oncol 15: 10-17, 1983.
Instructions for Authors 2016

General Policy. ANTICANCER RESEARCH (AR) will accept original high quality works and reviews on all aspects of experimental and clinical cancer research. The Editorial Policy suggests that priority will be given to papers advancing the understanding of cancer causation, and to papers applying the results of basic research to cancer diagnosis, prognosis, and therapy. AR will also accept the following for publication: (a) Abstracts and Proceedings of scientific meetings on cancer, following consideration and approval by the Editorial Board; (b) Announcements of meetings related to cancer research; (c) Short reviews (of approximately 120 words) and announcements of newly received books and journals related to cancer, and (d) Announcements of awards and prizes.

The principal aim of AR is to provide prompt publication (print and online) for original works of high quality, generally within 1-2 months from final acceptance. Manuscripts will be accepted on the understanding that they report original unpublished works in the field of cancer research that are not under consideration for publication by another journal, and that they will not be published again in the same form. All authors should sign a submission letter confirming the approval of their article contents. All material submitted to AR will be subject to review, when appropriate, by two members of the Editorial Board and by one suitable outside referee. The Editors reserve the right to improve manuscripts on grammar and style.

The Editors and Publishers of AR accept no responsibility for the contents and opinions expressed by the contributors. Authors should warrant due diligence in the creation and issuance of their work.

NIH Open Access Policy. The journal acknowledges that authors of NIH-funded research retain the right to provide a copy of the published manuscript to the NIH four months after publication in ANTICANCER RESEARCH, for public archiving in PubMed Central.

Copyright. Once a manuscript has been published in ANTICANCER RESEARCH, which is a copyrighted publication, the legal ownership of all published parts of the paper has been transferred from the Author(s) to the journal. Material published in the journal may not be reproduced or published elsewhere without the written consent of the Managing Editor or Publisher.

Format. Two types of papers may be submitted: (i) Full papers containing completed original work, and (ii) review articles concerning fields of recognisable progress. Papers should contain all essential data in order to make the presentation clear. Reasonable economy should be exercised with respect to the number of tables and illustrations used. Papers should be written in clear, concise English. Spelling should follow that given in the “Shorter Oxford English Dictionary”.

Manuscripts. Submitted manuscripts should not exceed fourteen (14) pages (approximately 250 words per double-spaced typed page), including abstract, text, tables, figures, and references (corresponding to 4 printed pages). Papers exceeding 4 printed pages will be subject to excess page charges. All manuscripts should be divided into the following sections:

(a) First page including the title of the presented work [not exceeding fifteen (15) words], full names and full postal addresses of all Authors, name of the Author to whom proofs are to be sent, key words, an abbreviated running title, an indication “review”, “clinical”, “epidemiological”, or “experimental” study, and the date of submission. (Note: The order of the Authors is not necessarily indicative of their contribution to the work. Authors may note their individual contribution(s) in the appropriate section(s) of the presented work); (b) Abstract not exceeding 150 words, organized according to the following headings: Background/Aim - Materials and Methods/Patients and Methods - Results - Conclusion; (c) Introduction; (d) Materials and Methods/Patients and Methods; (e) Results; (f) Discussion; (g) Acknowledgements; (h) References. All pages must be numbered consecutively. Footnotes should be avoided. Review articles may follow a different style according to the subject matter and the Author’s opinion. Review articles should not exceed 35 pages (approximately 250 words per double-spaced typed page) including all tables, figures, and references.

Figures. All figures should appear at the end of the submitted document file. Once a manuscript is accepted all figures and graphs should be submitted separately in either jpg, tiff or pdf format and at a minimum resolution of 300 dpi. Graphs must be submitted as pictures made from drawings and must not require any artwork, typesetting, or size modifications. Symbols, numbering and lettering should be clearly legible. The number and top of each figure must be indicated. Pages that include color figures are subject to color charges.

Tables. All tables should appear at the end of the submitted document file. Once a manuscript is accepted, each table should be submitted separately, typed double-spaced. Tables should be numbered with Roman numerals and should include a short title.

**Nomenclature and Abbreviations.** Nomenclature should follow that given in "Chemical Abstracts", "Index Medicus", "Merck Index", "IUPAC – IUB", "Bergey’s Manual of Determinative Bacteriology", The CBE Manual for Authors, Editors and Publishers (6th edition, 1994), and MIAME Standard for Microarray Data. Human gene symbols may be obtained from the HUGO Gene Nomenclature Committee (HGNC) (http://www.gene.ucl.ac.uk/). Approved mouse nomenclature may be obtained from http://www.informatics.jax.org/. Standard abbreviations are preferable. If a new abbreviation is used, it must be defined on first usage.

**Clinical Trials.** Authors of manuscripts describing clinical trials should provide the appropriate clinical trial number in the correct format in the text.

For International Standard Randomised Controlled Trials (ISRCTN) Registry (a not-for-profit organization whose registry is administered by Current Controlled Trials Ltd.) the unique number must be provided in this format: ISRCTNXXXXXXXX (where XXXXXXXXX represents the unique number, always prefixed by “ISRCTN”). Please note that there is no space between the prefix “ISRCTN” and the number. Example: ISRCTN47956475.

For Clinicaltrials.gov registered trials, the unique number must be provided in this format: NCTXXXXXXX (where XXXXXXX represents the unique number, always prefixed by 'NCT'). Please note that there is no space between the prefix 'NCT' and the number. Example: NCT00001789.

**Ethical Policies and Standards.** ANTICANCER RESEARCH agrees with and follows the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" established by the International Committee of Medical Journal Editors in 1978 and updated in October 2001 (www.icmje.org). Microarray data analysis should comply with the "Minimum Information About Microarray Experiments (MIAME) standard". Specific guidelines are provided at the "Microarray Gene Expression Data Society" (MGED) website. Presentation of genome sequences should follow the guidelines of the NHGRI Policy on Release of Human Genomic Sequence Data. Research involving human beings must adhere to the principles of the Declaration of Helsinki and Title 45, U.S. Code of Federal Regulations, Part 46, Protection of Human Subjects, effective December 13, 2001. Research involving animals must adhere to the Guiding Principles in the Care and Use of Animals approved by the Council of the American Physiological Society. The use of animals in biomedical research should be under the careful supervision of a person adequately trained in this field and the animals must be treated humanely at all times. Research involving the use of human foetuses, foetal tissue, embryos and embryonic cells should adhere to the U.S. Public Law 103-41, effective December 13, 2001.

**Submission of Manuscripts.** Please follow the Instructions for Authors regarding the format of your manuscript and references. Manuscripts must be submitted only through our online submission system at: http://www.iiar-submissions.com/login.html

In case a submission is incomplete, the corresponding Author will be notified accordingly.

Questions regarding difficulties in using the online submission system should be addressed to: email: journals@iiar-anticancer.org

**Galley Proofs.** Unless otherwise indicated, galley proofs will be sent to the corresponding Author of the submission. Corrections of galley proofs should be limited to typographical errors. Reprints, PDF files, and/or Open Access may be ordered after the acceptance of the paper. Authors of online open access articles are entitled to a complimentary online annual subscription to Anticancer Research for the current year. Requests should be addressed to the Editorial Office. Galley proofs should be returned corrected to the Editorial Office by email within two days.

**Specific information and additional instructions for Authors**

1. Anticancer Research (AR) closely follows the new developments in all fields of experimental and clinical cancer research by (a) inviting reviews on topics of immediate importance and substantial progress in the last three years, and (b) providing the highest priority for rapid publication to manuscripts presenting original results judged to be of exceptional value. Theoretical papers will only be considered and accepted if they bear a significant impact or formulate existing knowledge for the benefit of research progress.

2. Anticancer Research will consider the publication of conference proceedings and/or abstracts provided that the material submitted fulfils the quality requirements and instructions of the journal, following the regular review process by two suitable referees. (For further information please click here)

3. An acknowledgement of receipt, including the article number, title and date of receipt is sent to the corresponding author of each manuscript upon receipt. If this receipt is not received within 20 days from submission, the author should call or write to the Editorial Office to ensure that the manuscript (or the receipt) was not lost in the mail or during electronic submission.

4. Each manuscript submitted to AR is sent for review in confidence to two suitable referees with the request to return the manuscript with their comments to the Editorial Office within 12 days from receipt. If reviewers need a longer time or wish to send the manuscript to another expert, the manuscript may be returned to the Editorial Office with a delay. All manuscripts submitted to AR, are treated in confidence, without access to any person other than the Managing Editor, the journal's secretary, the reviewers and the printers.
5. All accepted manuscripts are peer-reviewed and carefully corrected in style and language, if necessary, to make presentation clear. (There is no fee for this service). Every effort is made (a) to maintain the personal style of the author's writing and (b) to avoid change of meaning. Authors will be requested to examine carefully manuscripts which have undergone language correction at the pre-proof or proof stage.

6. Authors should pay attention to the following points when writing an article for AR:

- The Instructions to Authors must be followed in every detail.
- The presentation of the experimental methods should be clear and complete in every detail facilitating reproducibility by other scientists.
- The presentation of results should be simple and straightforward in style. Results and discussion should not be combined into one section, unless the paper is short.
- Results given in figures should not be repeated in tables.
- Figures (graphs or photographs) should be prepared at a width of 8 or 17 cm with legible numbers and lettering.
- Photographs should be clear with high contrast, presenting the actual observation described in the legend and in the text. Each legend should provide a complete description, being self-explanatory, including technique of preparation, information about the specimen and magnification.
- Statistical analysis should be elaborated wherever it is necessary. Simplification of presentation by giving only numerical or % values should be avoided.
- Fidelity of the techniques and reproducibility of the results, should be points of particular importance in the discussion section. Authors are advised to check the correctness of their methods and results carefully before writing an article. Probable or dubious explanations should be avoided.
- Authors should not cite results submitted for publication in the reference section. Such results may be described briefly in the text with a note in parenthesis (submitted for publication by... authors, year).
- The References section should provide as complete a coverage of the literature as possible including all the relevant works published up to the time of submission.
- By following these instructions, Authors will facilitate a more rapid review and processing of their manuscripts and will provide the readers with concise and useful papers.

7. Following review and acceptance, a manuscript is examined in language and style, and galley proofs are rapidly prepared. Second proofs are not sent unless required.

8. Authors should correct their galley proofs very carefully and preferably twice. An additional correction by a colleague always proves to be useful. Particular attention should be paid to chemical formulas, mathematical equations, symbols, medical nomenclature etc. Any system of correction marks can be used in a clear manner, preferably with a red pen. Additions or clarifications are allowed provided that they improve the presentation but do not bring new results (no fee).

9. Articles submitted to AR may be rejected without review if:

- they do not fall within the journal's policy.
- they do not follow the instructions to authors.
- language is unclear.
- results are not sufficient to support a final conclusion.
- results are not objectively based on valid experiments.
- they repeat results already published by the same or other authors before the submission to AR.
- plagiarism is detected by plagiarism screening services.

(Rejection rate (2015): 64%).

10. Authors who wish to prepare a review should contact the Managing Editor of the journal in order to get confirmation of interest in the particular topic of the review. The expression of interest by the Managing Editor does not necessarily imply acceptance of the review by the journal.

11. Authors may inquire information about the status of their manuscript(s) by calling the Editorial Office at +30-22950-53389, Monday to Friday 9.00-16.00 (Athens time), or by sending an e-mail to journals@iil-anticancer.org

12. Authors who wish to edit a special issue on a particular topic should contact the Managing Editor.

13. Authors, Editors and Publishers of books are welcome to submit their books for immediate review in AR. There is no fee for this service.

(This text is a combination of advice and suggestions contributed by Editors, Authors, Readers and the Managing Editor of AR).

Copyright© 2016 - International Institute of Anticancer Research (J.G. Delinasios). All rights reserved (including those of translation into other languages). No part of this journal may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, microfilming, recording or otherwise, without written permission from the Publisher.