IJPSR (2012), Vol. 3, Issue 09 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 29 May, 2012; received in revised form 28 June, 2012; accepted 28 August, 2012

BIOMARKERS FOR THERAPEUTIC RESPONSE IN CERVICAL CANCER

Saleena Ummer V* and Asha Das

Department of MLT, Manipal College of Allied health Sciences, Manipal University, Manipal- 576 104 Karnataka, India

Keywords:
Cervical cancer,
Biomarker,
Therapeutic response,
Apoptotic markers,
Angiogenic markers

Correspondence to Author:

Saleena Ummer V

Assistant Professor, Department of MLT, Manipal College of Allied health Sciences, Manipal University, Manipal- 576 104 Karnataka, India

E-mail: finduvsaleena91@gmail.com

ABSTRACT

Cervical cancer, a potentially preventable disease, remains the second most common malignancy in women worldwide. Despite the tremendous progress that has been achieved in the screening and management of cervical cancer, there is still a need for clinically relevant prognostic biomarkers to monitor the response of patients to various therapies and to predict the chances of recurrence and recovery. Since cancer recurrence is the most common treatment failure in patients with advanced tumor, increasing knowledge about new biologic markers and better ability to predict risk of cancer recurrence is very important for construction of more effective treatment strategies. The biomarkers, which indicate the response of cancer patients to various therapy, predict response to particular therapies and choose the drug that, most likely to yield a favorable response in a given patient, identify patients with a high probability of adverse effects of a treatment and determine whether a therapy is having the intended effect on a disease and whether adverse effects arise. In this literature study we have done a survey of the identified biomarkers that will help in predicting therapeutic response of cervical cancer under the three classes, ie, apoptotic markers, angiogenic markers and other miscellaneous prognostic markers.

INTRODUCTION: Cervical cancer is the most common gynecologic malignancy in the world, and the second most frequently diagnosed cancer in women worldwide. Hence it continues to present a significant challenge to the health care community with approximately 471, 000 new cases diagnosed each year [1]. The growing risk of cervical cancer in women in India (aged 0-64 years) is 2.4% compared to 1.3% for the world [2].

As like any other cancers, stage of diagnosis is the most important prognostic factor in cervical cancer. Women diagnosed with early stage disease (IA-IB_1) have survival rate of 85-100%. Stage IIA tumors also have a good prognosis with a 5 year survival of approximately 90%. However once the tumor spreads further, the prognosis is poor. About 35% of women with cervical cancer will have persistent or recurrent disease [3]. Recurrences usually develop in the first 2 years after initial treatment. Hence close monitoring is recommended in patients receiving any type of treatment [4].

QUICK RESPONSE CODE

IJPSR: ICV- 4.57

Website: www.ijpsr.com

Understanding the molecular basis of the biochemical pathways involved in cervical cancer can facilitate the integration of diagnosis, anticancer drug discovery, therapy for cancer and its monitoring. Prognostication and the variability of tumor responses to radio-/chemo-therapeutic agents is a topic of major interest in current cancer research. A biomarker might be either a molecule secreted by tumor itself, or it can be a specific response of the body to the presence of cancer. Genetic, epigenetic, proteomic, glycomic, and imaging biomarkers can be used for cancer diagnosis as well as prognosis.

As an important biological indicator of cancer status, progression and for the physiological state of the cell at a specific time, biomarkers represent powerful tools for monitoring the course of cancer and gauging the efficacy and safety of novel therapeutic agents. They can have tremendous therapeutic impact in clinical oncology, especially if the biomarker is detected before clinical symptoms or enable real-time monitoring of drug response. The challenge in the field of biomarkers is to develop methodology that will allow us to use the available knowledge and tools to evaluate the usefulness of molecular abnormalities for improving individual and population outcomes for cervical cancer [5].

Since cancer recurrence is the most common treatment failure in patients with advanced tumor, increasing knowledge about new biologic markers and better ability to predict risk of cancer recurrence is very important for construction of more effective treatment strategies. Biomarkers help to identify genetic variations or mutations as well as changes in gene or protein expression or activity that can be linked to a disease state or a response to a medical intervention [6].

The biomarkers, which indicate the response of cancer patients to various therapy, predict response to particular therapies and choose the drug that, most likely to yield a favorable response in a given patient, identify patients with a high probability of adverse effects of a treatment and determine whether a therapy is having the intended effect on a disease and whether adverse effects arise [7]. In this literature study, we have done a survey of the identified biomarkers.

Biomarkers can be either molecular biomarkers or imaging biomarkers. Prognostic markers separate patients with good and bad prognosis to aid the decision about how aggressive the therapy needs to be. It also provides clues for the possible mechanism(s) responsible for the poor prognosis which helps in identification of new targets for therapy. A predictive marker on the other hand, identifies how likely an individual is to respond to a particular therapy before initiation of treatment [8].

Prior to discussing individual biomarkers utilized, it is important to note how the performance of biomarkers is evaluated. Biomarker test performance is characterized by measures of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) with the area under receiver operating characteristic curve (AUC). Detection of biomarkers, either individually or as larger sets or patterns, can be accomplished by a wide variety of methods, ranging from biochemical analysis of blood or tissue samples to biomedical imaging, which include, spectrophotometry, ELISA, DNA arrays, sequencing methods, mass spectrometry, liquid chromatography and protein sequencing [6, 8].

Apoptotic Markers in Cervical Cancer: Apoptotic markers are indicators of the process of apoptosis which is an essential mechanism to prevent the proliferation of cells with a higher mutation rate, thus tempering malignant transformation.

1. **ERCC 1 expression:** Excision Repair Cross-Complementation group 1 enzyme (ERCC1) is a molecular marker which can be used to rapidly evaluate the cisplatin responsiveness of cervical tumors. Cisplatin is a valuable adjuvant to radiotherapy for the treatment of cervical cancer. ERCCI encoded by the ERCC1 gene, is a key enzyme in the nucleotide excision repair pathway which is involved in the DNA repair mechanisms in tumor cells damaged by treatment with platinum agents.

   Preclinical and clinical data have suggested a potential use of ERCC1 as a molecular predictor of clinical resistance to platinum-based chemotherapy. Higher expression level of ERCC1 is significantly associated with platinum drugs resistance [9] and it has been proved that

ERCC1 mRNA levels are also having significant correlation with cisplatin resistance [10]. Since the correlation between ERCC1 mRNA levels and cisplatin resistance in single-cell-derived cervical carcinoma cell lines that exhibit a wide range of inherent sensitivity to cisplatin is proved, pre-treatment ERCC1 mRNA level is a useful predictive indicator for tumor-cell/clinical response to cisplatin-based chemotherapy [11].

2. **Protein 53 (p 53):** p53 (protein 53 or tumor protein 53), is a tumor suppressor protein that in humans is encoded by the TP53 gene. p53 is known to be a cell cycle checkpoint protein and thus functions as a tumor suppressor playing a regulatory role in the control of cell proliferation and apoptosis thereby preventing cancer. If the p53 gene is damaged, tumor suppression is severely reduced [12, 13]. The loss, or inactivation, of wild-type p53 has been found to indirectly promote tumor angiogenesis by up-regulation of angiogenesis-promoting protein, the vascular endothelial growth factor (VEGF) [14].

3. **Clusterin:** Clusterin has been implicated in a variety of activities including programmed cell death, regulation of complement mediated cell lysis, membrane recycling, cell to cell adhesion and Src induced transformation. Overexpression of clusterin, an anti-apoptotic molecule, has been reported to induce resistance to chemotherapy in a variety of cancer cell types. Clusterin induce resistance by physically binding to paclitaxel, which may prevent paclitaxel from interacting with microtubules to induce apoptosis [15].

   The increased expression of clusterin in cervical cancer tissues than in normal cervical tissues in different studies, suggests that clusterin may confer paclitaxel resistance in cervical cancer cells [16]. Clusterin expression could be a new molecular marker to predict response to platinum-based chemotherapy and survival of patients with cervical cancer treated with neo-adjuvant chemotherapy and radical hysterectomy.

4. **Parathyroid Hormone Related Peptide (PTHrP):** Parathyroid hormone-related protein (or PTHrP) is a protein member of the parathyroid hormone family. It is occasionally secreted by cancer cells. It regulates endochondral bone development by maintaining the endochondral growth plate at a constant width. It also regulates epithelial-mesenchymal interactions during the formation of the mammary glands.

   PTHrP induces chemoresistance by interference with p53 family-dependent apoptosis signaling pathways and p53-mediated transactivation of apoptosis target genes. PTHrP inhibits major apoptosis signaling pathways by blocking signaling via p53, death receptors and mitochondria and consequently confers chemoresistance of cancer cells [17].

5. **Serum Nucleosomes:** In patients with cancer, there is often a correlation between tumor load and amount of free DNA in circulation that at least part is present in the form of oligo- and mononucleosomes, as a marker of cell death. Serum nucleosome level determined in the third course of neoadjuvant chemotherapy in patients with cervical cancer is marginally related with tumor response and survival. Serum nucleosomes may have a predictive role for response and prognostic significance in patients with cervical cancer patients treated with neoadjuvant chemotherapy [18].

6. **Cytokeratins:** The level of cytokeratin-19 in cervical cancer cells will be decreased. The reduction of cytokeratin-19 level has a killing effect on cervical carcinoma SiHa and HeLa S3 cell lines. The apoptotic rate of cervical carcinoma cells in response to cisplatin and vinblastin will be increased if their cellular cytokeratin-19 level is reduced by specific antibody MAb Cx-99. This indicates that elevation of cytokeratin-19 expression could associate with the apoptotic resistance and malignant progression of cervical carcinoma [19].

   The LD80 values were at least 15-fold reduced when cancer cells were treated with cisplatin or vinblastine in the presence of MAb Cx-99. These results suggest that the functional role of cytokeratin-19 is associated with the apoptosis resistance and thus leads to drug resistance of cervical cancer cells [20].

7. **Bax Gene:** Bax can function as an effector of p53 in chemotherapy-induced apoptosis and contributes to a p53 pathway to suppress oncogenic transformation thus becoming a determinant of p53-dependent chemosensitivity [21]. HPV-positive cervical tumors were shown to undergo apoptosis upon expression of Bax, a molecule directly regulated by functional p53 proving its role in apoptosis and sensitivity to chemotherapy [22, 23].

   Patients in whom BOAI (cisplatin-based cyclic balloon-occluded arterial infusion chemotherapy) is effective will show significantly higher expression of the bax protein and gene after BOAI, and cancer cell apoptosis will be accelerated. On the other hand, patients in whom BOAI is ineffective will show significantly higher expression of the bcl-xL protein and gene after BOAI. Thus bax/bcl-xL expression can be used as an indicator of the effectiveness of BOAI therapy [24]. In conclusion, increased Bax expression results in good response to chemotherapy.

8. **Survivin:** Survivin is a structurally unique member of the inhibitors of apoptosis protein (IAP) family that is involved in both control of cell division and inhibition of apoptosis. The survivin protein is expressed highly in most human tumors and fetal tissue, but is completely absent in terminally differentiated cells. *In-vitro* and *in-vivo* studies targeting survivin with antisense oligonucleotides have shown that negative mutants or ribozymes induce apoptosis, reduce tumour-growth potential and sensitise tumour cells to chemotherapeutic drugs such as taxol, cisplatin, etoposide, γ-irradiation, and immunotherapy. Study of the markers of survival demonstrated that survivin expression correlates with drug resistance in CaSki and SiHa cells [25].

9. **Bcl – xL (B-cell lymphoma-extra-large):** It is one of several anti-apoptotic proteins which are members of the Bcl-2 family of proteins. It has been implicated in the survival of cancer cells. Increased expression of antiapoptotic BAG-1, p50, p33 and Bcl-xL may cause resistance to apoptosis through reduction of caspase-3 activity in human cervical cells having an MDR phenotype [26]. Increased levels of Bcl-xL in the HPV16-immortalized and the CSC-transformed HEN, correlated with progressively increased resistance of these cells to apoptosis induced by staurosporine or cisplatin [27]. The ability of bcl-xL to prevent apoptotic cell death in response to chemotherapy-induced DNA damage and cell-cycle arrest may contribute to the accumulation of chromosomal aberrations within tumors. The expression of bcl-xL in tumor cells is likely to be an important indicator of chemotherapeutic efficacy [28].

10. **mTOR:** The mammalian target of rapamycin (mTOR) also known as FK506 binding protein 12-rapamycin associated protein 1 (FRAP1) is a protein which in humans is encoded by the FRAP1 gene. The expression of phosphorylated mTOR may have a role as a marker to predict response to chemotherapy and survival of cervical cancer patients who are treated with cisplatin-based neoadjuvant chemotherapy. *In vitro* studies have shown that pretreatment with rapamycin inhibited activation of mTOR signaling and significantly enhanced the sensitivity of CaSki cells to paclitaxel by increasing apoptotic cell death. Thus, mTOR inhibitors enhance chemosensitivity of paclitaxel and cisplatin in ovarian and cervical cancer cells [29]. The mTOR cascade may be a promising target for therapeutic intervention in cervical cancer. These studies address potential of targeting mTOR protein in the enhancement of therapeutic efficacy of chemotherapy in human cervical cancer [30].

Angiogenic Markers: Angiogenesis is essential for the growth of solid tumors. Tumor hypoxia and progression of cervical cancer seems to correlate with the angiogenic potential of the tumor. High blood vessel density predicts improved survival with radiotherapy and chemotherapy.

1. **Cycloxygenase (cox)-2:** Cyclooxygenase (COX) is an enzyme that is responsible for the formation of prostanoids**.** Two cyclooxygenase isoforms that have been identified are COX-1 which is produced constitutively (i.e., gastric mucosa) and COX-2 which is inducible (i.e., sites of inflammation) by the action of macrophages. Cycloxygenase 2 (COX-2) is an important marker for predicting response of cervical cancer to adjuvant chemotherapy. COX-

2 levels significantly correlates with VEGF levels in uterine cervical cancers. VEGF associated with COX-2 might work in the advancement of angiogenesis [31]. The expression of COX-2 has been shown to be induced by proinflammatory cytokines, and suggestions have been made that overexpression of COX-2 suppresses apoptosis and is directly related to tumor growth. The expression of COX-2 in stage IB cervical cancer may down regulate apoptotic processes and thus enhances tumor invasion and metastasis [32].

2. **Thymidine Phosphorylase (dThdPase or TP):** dThdPase gene and protein expression levels in cervical carcinoma cell lines were closely related to the number of cells that migrated and invaded. Studies also suggest that dThdPase expression may be closely related to tumor invasion and metastasis[33]. Immunohistochemical expression of TP in tumor cells has been suggested as a useful prognostic factor for uterine cervical squamous cell carcinomas treated with radiotherapy. Choosing therapy for individual cases by referring to factors including TP expression should contribute to an improved prognosis [34].

3. **Major Vault Protein (MVP):** Hypoxia induces drug resistance in clinical tumours. Vaults are multi sub unit structures which mediate bidirectional nucleocytoplasmic transport of a wide range of substrates, including cytotoxic drugs. Chemo-resistance would be mediated by up-regulation of Major Vault Protein (MVP) through the Hypoxia-inducible factor 1 (HIF-1). Increased levels of MVP have been reported in numerous cell lines after treatment with a wide panel of cytostatic drugs like doxorubicin, methotrexate, vincristine or cisplatin [35].

   Thus over-expression of MVP has been associated with chemotherapy resistance. MVP over-expression was associated with reduced long-term local control in patients who achieved clinical complete response to radio-chemotherapy [36].

4. **Vascular Endothelial Growth Factor (VEGF):** Vascular endothelial growth factor (VEGF) is a chemical signal produced by cells that stimulates the growth of new blood vessels. VEGF production is considered essential for angiogenesis and cancer metastasis, with high titres being indicative of a poor prognosis [37]. Patients with cervical cancer who are positive for VEGF expression are less likely to benefit from neoadjuvant chemotherapy. Pretreatment assessment of VEGF expression may provide additional information for identification of patients with cervical cancer who had a low likelihood of response to neoadjuvant chemotherapy and an unfavorable prognosis.

5. **CD31 (PECAM-1):** CD31 is a member of the adhesion molecule family and is also known as platelet endothelial cell adhesion molecule-1 (PECAM-1) or endothelial cell adhesion molecule (endoCAM-1). It plays a key role in removing aged neutrophils from the body. CD31 has been used to measure angiogenesis, which reportedly predicts tumor recurrence. Micro Vascular Density (MVD) is assumed to reflect the intensity of tumor angiogenesis; indeed, it has been established as a good indicator of prognosis in several cancer types.

   If validated, CD31 MVD has the potential to identify a group of women who are less likely to benefit from standard adjuvant chemoradiotherapy and might be better served with neoadjuvant chemotherapy and surgery, with a new radiosensitizing regimen like cisplatin and tirapazamine or an anti-angiogenesis drug like bevacizumab which exhibited single-agent activity in recurrent cervical cancer [35, 38].

   High CD31 MVD is not only associated with prolonged Progression-free survival (PFS) and Overall survival (OS)but is an independent prognostic factor in women with high-risk, early stage cervical cancer treated with radiation therapy alone or chemoradiation. High CD31 MVD is a surrogate marker for improved tumor blood flow and oxygenation, resulting in a better response to adjuvant radiotherapy with chemotherapy [38].

Other Prognostic Markers:

1. **P- Glycoprotein:** Many cancers fail to respond to chemotherapy by acquiring multi drug resistance (MDR) to which it has been attributed the failure of treatment in over 90% of patients with metastatic cancer. Although MDR can have several causes,

one major cause of multi drug resistance is the presence of molecular "pumps" that transport drugs out of the cell. The most prevalent of these MDR transporters is P-glycoprotein, a particularly "promiscuous" molecule that transports distinct types of molecules ranging from peptides to steroids as well as chemotherapy drugs. Once a cancer cell starts to produce P-gp it becomes resistant to chemotherapy drugs and it becomes much less likely that the patient will recover [39].

P-glycoprotein was found to be increased in radical hysterectomy samples from locally advanced or bulky cervical carcinoma treated with two courses of intraarterial infusion of cisplatin, doxorubicin, mitomycin C, and 5-fluorouracil (5-FU), when compared with pretreatment biopsy. Assessment of the expression of P-glycoprotein is thus potentially useful for the prediction of tumor response to neoadjuvant chemotherapy for cervical carcinomas [40].

2. **Carcinoembryonic Antigen (CEA):** Carcinoembryonic Antigen (CEA) is a glycoprotein which is produced in significant amounts by the large intestine during fetal development. Chemotherapy and radiation therapy can cause a temporary rise in CEA due to the death of tumor cells and release of CEA into the blood stream. Benign disease does not usually result in an increase above 10 ng/ml. CEA is a valuable tumor marker to predict the prognosis of squamous cell carcinoma of the uterine cervix and to foresee a clinical response to subsequent neoadjuvant chemotherapy [41]. Kjorstad and Orjasaester have reported that all the patients with pre-treatment levels over 15ug/l died during the follow up. In the range between 5-15ug/l, two third of them developed recurrence [42].

3. **Squamous Cell Carcinoma Antigen (SSCA):** SCCA belongs to the family of serine and cysteine protease inhibitors. It is a protein that in humans is encoded by the SERPINB4 gene. This antigen is present in normal cervix epithelium with an increased expression in proportion to dysplastic lesion and cervical squamous cell carcinoma. Approximately 60% of patients with cervical cancer are detected with elevated levels of serum SCCA at initial diagnosis, when all stages are included. Several studies have concluded that serum SCCA is useful in monitoring the course of squamous cell cervical cancer following primary therapy. Persistently elevated serum SCCA levels after and/or during treatment suggest tumor persistence or progressive disease especially in distant metastatic sites [43]. Levels of antigen prior to chemotherapy may not predict the response to treatment, but patients whose levels decrease during chemotherapy are more likely to show responses to treatment and the antigen levels are more predictive of response after two cycles of chemotherapy than one [44]. SCC assay may provide useful information to improve the prognostic characterization and disease monitoring of patients with locally advanced cervical cancer undergoing neoadjuvant chemotherapy [45].

4. **Thymidylate Synthase (TS):** Thymidylate synthase (EC2.1.1.45) is the enzyme used to generate thymidine monophosphate (dTMP), which is subsequently phosphorylated to thymidine triphosphate for use in DNA synthesis and repair. Certain germline polymorphisms in TS have been shown to influence the level of TS expression which supports the hypothesis that genotyping patients for TS polymorphisms may also serve as a useful predictive marker of fluoropyrimidine response and toxicity [46] and unlike the determination of intratumoral gene expression which requires available tumor tissue, genotyping can be performed on blood, which is more readily available. Those tumors with high TS gene expression are generally non-responsive to protocols that include the TS-directed combination of 5-FU and leucovorin [47].

5. **Dihydropyramidine Dehydrogenase (DPD):** Dihydropyrimidine dehydrogenase (DPD) is an enzyme that is involved in pyrimidine degradation. It is also involved in the degradation of the chemotherapeutic drugs like 5-fluorouracil and Tegafur-uracil. Individuals with Dihydropyrimidine dehydrogenase deficiency may develop life-threatening toxicity following exposure to 5-fluorouracil (5-FU) or oral fluoropyrimidine capecitabine (Xeloda) because the drugs are not at all degraded. Patients with low expression levels of

DPD are more likely to respond to 5-FU therapy [48]. Study on Thymidine phosphorylase/Dihydro-pyrimidine dehydrogenase (TP/DPD) ratio showed significantly higher disease -free survival rate in patients with low TP/DPD levels indicating that this ratio may be associated with both progression and recurrence of invasive cervical cancer [49].

6. **X-Ray Repair Cross Complementing Protein 1(XRCC1):** The protein encoded by this gene is involved in the efficient repair of DNA single-strand breaks formed by exposure to ionizing radiation and alkylating agents. This protein interacts with DNA ligase III, polymerase beta and poly (ADP-ribose) polymerase to participate in the base excision repair pathway. Genetic polymorphism of XRCC1 R399Q is associated with response to platinum-based NAC in bulky cervical cancer, and MDR analysis documented association between gene-gene interaction of XRCC1 R399Q and treatment response [50].

7. **NF-κB (Nuclear Factor Kappa-Light-Chain-Enhancer Of Activated B Cells):** NF-κB is a protein complex that controls the transcription of DNA and plays a key role in regulating the immune response to infection. Conversely, incorrect regulation of NF-κB has been linked to cancer, inflammatory and autoimmune diseases. If treated with a small molecule inhibitor towards aurora kinases, (which helps in cellular division by controlling chromatid segregation), the NF-κB activity will be down regulated and the efficacy of cytotoxic drugs will be enhanced. This shows that there is an association between cell resistance to chemotherapeutic agents and NF-κB activation [51].

8. **c-erbB-2 Oncoprotein:** c-erbB-2 oncoprotein is a 185 KDa membrane bound glycoprotein. It is a receptor on the cytoplasmic membrane which is homologous to the epidermal growth factor receptor (c-erbB-1). c-erbB-2 oncoprotein is associated with a reduced response to neo-adjuvant chemotherapy in the primary treatment of invasive cervical cancer. Thus, over expression of c-erbB-2 can be used as a useful marker to identify patients who are likely to benefit from high doses of adjuvant chemotherapy [52].

9. **Cadherin Methylation:** Cadherins (Calcium dependent adhesion molecules) are a class of type-1 transmembrane proteins. They play important roles in cell adhesion, ensuring that cells within tissues are bound together. Inactivation of the cadherin-mediated cell adhesion system, caused by aberrant methylation, is a common finding in human cancers. Detection of aberrant cadherin methylation may be of potential use as a marker for selecting cervical cancer patients at high risk for relapse who could benefit from additional systemic therapy [53].

CONCLUSION: Biomarker research has become a sign of the times, and the identified biomarkers can be used for relating patient's response to drugs. The drug-related biomarkers indicate whether a drug will be effective in a specific patient and how the patient's body will process it. Prognostic biomarkers help devising an optimal therapeutic treatment plan for different patient subsets and to monitor the effect of treatment. It is becoming clear that mapping the entire networks rather than individual markers may be necessary for robust diagnostics and tailoring of therapy.

Genomics offers the opportunity to examine gene expression or the variation in gene sequence, whereas proteomics encompasses evaluation of protein expression, activation, modification, degradation, and ambitiously targets protein function. In years to come, a serum or urine test for every phase of cancer may drive clinical decision making, supplementing or replacing currently existing invasive techniques.

Advances in the field of biomarkers will enable techniques to be developed that can profile tumor cells for their genetic background, allowing selection of anticancer agents on an individual basis. The next generation of anticancer treatments might therefore be tailored according to the molecular alterations identified in tumor cells of individual patients.

REFERENCES:

1. European Society For Medical Oncology Handbook Of Cancer Prevention by Dirk Schrijvers, Hans-jorg Senn, Hakan Mellstedt, Branko Zakotnic
2. Jacqueline Sherris, Cristina Herdman, and Christopher Elias, President Cervical cancer in the developing world West J Med. 2001 October; 175(4): 231–233.

3. Greer BE, Koh WJ. (2002). Diagnosis and treatment of cervical carcinomas. American College of Obstetricians and Gynecologists, 99(5): 855–866
4. Janicek MF, Averette HE. (2001). Cervical cancer: Prevention, diagnosis, and therapeutics. CA, A Cancer Journal for Clinicians, 51: 92–114.
5. Contribution of oncoproteomics to cancer biomarker discovery William CS Cho Molecular Cancer 2007, 6:25
6. Translating Biomarker Discovery to Clinical Application, Sudhir Srivastava, Ph.D., M.P.H. Cancer Biomarkers Research Group
7. A.-E. Konstantinidou, P. Korkolopoulou and E. PatsourisApoptotic markers for tumor recurrence: A minireviewApoptosisVolume 7, Number 5 / October, 2002
8. Aronson, J. K. (2008) Biomarkers and Surrogate Endpoints in Monitoring Therapeutic Interventions, Evidence-based Medical Monitoring: From Principles to Practice (eds P. P. Glasziou, L. Irwig and J. K. Aronson), Blackwell Publishing Ltd, Oxford, UK
9. Britten, r.a., evans, a.j., allalunis-turner, m.j.and pearcey,r.g.effect of cisplatin on the clinically relevant radiosensitivity of human cervical carcinoma cell lines. Int. J. Radiat. Oncol. Biol. Phys., 34, 367-374 (1996b).
10. Dijt, F.J., Fichtinger-Schepman, A.M.J., Berends, F. And Reedijk, J., Formation and repair of cisplatin-induced adducts to dna in cultured normal and repair-deficient human fibroblasts. Cancer res., 48, 6058–6062 (1988).
11. Metzger, R. And 14 others, ercc1 levels complement thymidylate synthase mrna levels in predicting response and survival for gastric cancer patients receiving combination cisplatin and fluorouracil chemotherapy.j. Clin. Oncol., 16, 309–316 (1998).
12. Villa LL. Human papilloma viruses and cervical cancer. Adv Cancer Res 1997; 71: 321–341. 14.
13. Scheffner M. Ubiquitin, E6-AP, and their role in p53 inactivation. Pharmacol Ther 1998; 78: 129–139
14. Lee JS, Kim HS, Park JT, et al. Expression of vascular endothelial growth factor in the progression of cervical neoplasia and its relation to angiogenesis and p53 status. Anal Quant Cytol Histol 2003; 25:303
15. Park Dong Choon; Yeo Seung Geun; Wilson Mark R; Yerbury Justin J; Kwong Joseph; et al, Clusterin interacts with Paclitaxel and confer Paclitaxel resistance in overian cancer. Neoplasia, 2008;10(9):964-72
16. Dong Choon Park, Seung Geun Yeo, Eun Young Shin, Samuel C. Mok et al, Clusterin confers paclitaxel resistance in cervical cancerGynecologic Oncology, Volume 103, Issue 3, December 2006, 996-1000
17. Sarah Gagiannis , Martina Müller , Sebastian Uhlemann , Andreas Koch , Gerry Melino , Peter H. Krammer , et al, Parathyroid hormone-related protein confers chemoresistance by blocking apoptosis signaling via death receptors and mitochondria International Journal of Cancer Volume 125 Issue 7, Pages 1551 – 1557
18. Catalina Trejo-Becerril, Luis F Oñate-Ocaña, Lucía Taja-Chayeb,América Vanoye-Carlo, Lucely Cetina,and Alfonso Duenas-GonzalezSerum nucleosomes during neoadjuvant chemotherapy in patients with cervical cancer. Predictive and prognostic significanceBMC Cancer 2005; 5: 65
19. Yuan CC, Huang HC, Tsai LC, Ng HT, Huang TS. Cytokeratin-19 associated with apoptosis and chemosensitivity in human cervical cancer cells. Apoptosis. 1997;2:101–5.
20. C-C. Yuan, T-S. Huang, H-T Ng, R-S. Liu, M-W. Hung and L-C. Tsai Elevated cytokeratin-19 expression associated with apoptotic resistance and malignant progression of human cervical carcinoma Apoptosis Volume 3, Number 3 / June, 1998
21. Mila E. McCurrach, Thomas M. F. Connor, C. Michael Knudson†,Stanley J. Korsmeyer†, and Scott W. Lowebax-deficiency promotes drug resistance and oncogenic transformation by attenuating p53 dependent apoptosis Cell Biology Vol. 94, pp. 2345–2349, March 1997
22. McCurrach ME, Connor TM, Knudson CM et al. Bax-deficiency promotes drug resistance and oncogenic transformation by attenuating p53-dependent apoptosis. Proc Natl Acad Sci USA 1997; 94: 2345– 2349.
23. McPake CR, Tillman DM, Poquette CA et al. Bax is an important determinant of chemosensitivity in pediatric tumor cell lines independent of Bcl-2 expression and p53 status. Oncol Res 1998; 10: 235–244.
24. Okamto Eri; Sumi Toshiyuk: Misugui Fumiko; Nobeyama Hiroyuki;Hattori Kanae; Yoshida Hiroyuki; Matsumoto Yoshinari; Yasui Tomoyo; Honda Ken-Ichi; Ishiko Osamu. Expression of apoptosis-related proteins in advanced uterine cervical cancer after balloon-occluded arterial infusion chemotherapy as an indicator of the efficiency of this therapy International journal of molecular medicine, vol. 15, n1, pp. 41-47
25. Nadia Zaffaroni, Maria Grazia DaidoneSurvivin expression and resistance to anticancer treatments: perspectives for new therapeutic interventions.Drug resistance updates. Volume 5, Issue 2, 65-72 (April 2002)
26. Ding Z, Yang X, Pater A, Tang SC (2000) Resistance to apoptosis is correlated with the reduced caspase-3 activation and enhanced expression of antiapoptotic proteins in human cervical multidrug-resistant cells. Biochem Biophys Res Commun 270, 415-20
27. Yang X, Hao Y, Pater MM, Tang SC, Pater A.Enhanced expression of anti-apoptotic proteins in human papillomavirus-immortalized and cigarette smoke condensate-transformed human endocervical cells: correlation with resistance to apoptosis induced by DNA damage.
28. Minn, CM Rudin, LH Boise and CB Thompson Expression of bcl-xL can confer a multidrug resistance phenotype Blood.Journal of the American society of hematology Volume 86, Issue 5, pp. 1903-1910, 09/01/1995
29. H, Minegishi T. Inhibition of the mammalian target of rapamycin (mTOR) by rapamycin increases chemosensitivity of CaSki cells to paclitaxel. Eur J Cancer 42: 934-947, 2006.
30. Faried LS, Faried A, Kanuma T, Nakazato T, Tamura T, Kuwano H, Minegishi T. Inhibition of the mammalian target of rapamycin (mTOR) by rapamycin increases chemosensitivity of CaSki cells to paclitaxel. Eur J Cancer 42: 934-947, 2006
31. Jiro Fujimoto, Hiroshi Toyoki, *et al*, Expression of cyclooxygenase-2 related to angiogenesis in uterine cervical cancers Journal of Biomedical Science (2006) 13:825–832
32. 325Hee-Sug Ryu M.D., Ki-Hong Chang M.D., Hyun-Won Yang Ph.D., Myung-Shin Kim M.S., Hyuck-Chan Kwon M.D. and Kie-Suk Oh M.DHigh Cyclooxygenase-2 Expression in Stage IB Cervical Cancer with Lymph Node Metastasis or Parametrial Invasion Gynecologic Oncology Volume 76, Issue 3, March 2000, Pages 320-325
33. Sato S, Yajima A, Sasaki H, Mizutani K, Honjo H, Yamamoto K, Ozaki M, Hasegawa K, Kudo T, Yakushiji M, Hatae M, Noda K. Prognostic value of thymidine phosphorylase immunostaining in patients with uterine cervical cancer treated concurrently with doxifluridine, radiotherapy and immunotherapy. Oncol Rep. 2001 Mar-Apr; 8(2):239-44.
34. Masatsugu Ueda, Ken Ueki, Koji Kumagai, Yoshito Terai, Yoshiaki Okamoto, Minoru Ueki and Yoshinori OtsukiApoptosis

and Tumor Angiogenesis in Cervical Cancer after Preoperative Chemotherapy Cancer Research 58, 2343-2346, June 1, 1998
35. Lange C, Walther W, Schwabe H, Stein U: Cloning and initial analysis of the human multidrug resistance-related MVP/LRP gene promoter.Biochem Biophys Res Commun 2000, 278:125-133
36. Lloret M, Lara PC, Bordon E, Rey A, Falcon O, Apolinario RM, Clavo B, Ruiz A: MVP expression is related to IGF1-R in cervical carcinoma patients treated by radiochemotherapy. Gynecol Oncol 2008, 110:304-307.
37. Toi M, Matsumoto T, Bando H. Vascular endothelial growth factor: its prognostic, predictive, and therapeutic implications. Lancet Oncol. 2001;2:667–673.
38. Monk BJ, Sill MW, Burger RA. Phase II trial of bevacizumab in the treatment of recurrent squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. Gynecologic Oncology 2008;108:S23
39. S.G. Aller, J. Yu, A. Ward, Y. Weng, S. Chittaboina, R. Zhuo, P.M. Harrell, et al, "Structure of P-glycoprotein reveals a molecular basis for poly-specific drug binding," Science 323, 1718 (2009)
40. Ikuo Konishi M.D., Kanako Nanbu M.D., Masaki Mandai M.D.et al, Tumor Response to Neoadjuvant Chemotherapy Correlates with the Expression of P-Glycoprotein and PCNA but Not GST-π in the Tumor Cells of Cervical CarcinomaGynecologicOncology Volume 70, Issue 3, September 1998, 365-371
41. Bae SN, Namkoong SE, Jung JK, Kim CJ, Park JS, Kim JW, Lee JM, Kim SJ: Prognostic significance of pre-treatment squamous cell carcinoma antigen and carcinoembryonic antigen in squamous cell carcinoma of the cervix. Gynecol Oncol Mar;64(3):418-24, 1997
42. Kjorstad K.E and Orjasaester, H: The prognostic significance of carcinoembryonic antigen determinations in patients with adenocarcinoma of the cervix Gynaecologic Oncology, 19:284-289, 1984 ,
43. Ngan, H. Y. S.; Cheng, G. T. S.; Cheng, D.; Wong, L. C.; Ma, H. K. Post-treatment serial serum squamous cell carcinoma antigen (SCC) in the monitoring of squamous cell carcinoma of the cervix international Journal of Gynecological Cancer: March-april 1996 - Volume 6 - Issue 2 - 115-119
44. Panici, Pierluigi B, Mancuso, Salvatore, Scambia, et al, The value of squamous cell carcinoma antigen in patients with locally advanced cervical cancer undergoing neoadjuvant chemotherapy. Am J Obstet Gynecol. 1991 Feb; 164(2):631-6.
45. Scambia G, Benedetti Panici P, Foti E, Amoroso M, Salerno G, Ferrandina G, Battaglia F *et al*, Squamous cell carcinoma antigen: prognostic significance and role in the monitoring of neoadjuvant chemotherapy response in cervical cancer. J Clin Oncol. 1994 Nov;12(11):2309-16.
46. Agustin A. Garcia, M.D. John A. Blessing, Ph.D., Kathleen M. Darcy, Ph.D., et al, Phase II clinical trial of capecitabine in the treatment of advanced ,persistent or recurrent squamous cell carcinoma of the cervix with translational research:A gynecologic oncologic group study Gynecol Oncol. 2007 March; 104(3): 572–579.
47. Santin, A. D., Hermonat. P. L., Ravaggi, A., Chiriva-Internati, M., Pecorelli, S., Parham, G. P. (1998) Radiation-enhanced expression of E6/E7 transforming oncogenes of human papillomavirus-16 in human cervical carcinoma. Cancer 83, 2346–2452
48. Agustin A. Garcia, M.D. John A. Blessing, Ph.D., Kathleen M. Darcy, Ph.D., et al, Phase II clinical trial of capecitabine in the treatment of advanced ,persistent or recurrent squamous cell carcinoma of the cervix with translational research:A gynecologic oncologic group study Gynecol Oncol. 2007 March; 104(3): 572–579.
49. Junichi Kodama, Hasengaowa, Yasuhiro Shinyo, Tomoyuki Kusumoto, Noriko Seki, Yojiro Nakamura, Keiichiro Nakamura, Atsushi Hongo, Yuji Hiramatsu Prognostic significance of the thymidine phosphorylase/dihydropyrimidine dehydrogenase ratio in invasive cervical cancerVolume 121, Issue 1, 81-85
50. Chung HH, Kim MK, Kim JW, et al, XRCC1 R399Q polymorphism is associated with response to platinum-based neoadjuvant chemotherapy in bulky cervical cancer .Gynecol Oncol. 2006 Dec; 103(3):1031-7.
51. Chongbo Sun, Florence Chan, Paraskevi Briassouli et al, Aurora kinase inhibition downregulates NF-κB and sensitises tumour cells to chemotherapeutic agentsBiochemical and Biophysical Research Communications Volume 352, Issue 1, 5 January 2007, Pages 220-225
52. Jae Wook Kim, Young Tae Kim, and Dong Kyu Kim; Correlation between EGFR and c-erbB-2 Oncoprotein Status and Response to Neoadjuvant Chemotherapy in Cervical Carcinoma ;Yonsei Med J 1999 June; 40(3):207-214
53. Andreas Widschwendter , Lennart Ivarsson , Anya Blassnig , Hannes M. Müller , et al, CDH1 and CDH13 methylation in serum is an independent prognostic marker in cervical cancer patients; International Journal of Cancer Volume 109 Issue 2, 163 - 166

How to cite this article:
Ummer V S and Das A: Biomarkers for Therapeutic Response in Cervical Cancer. *Int J Pharm Sci Res*, 2012; Vol. 3(9): 3036-3044.