Targeted Therapy in Cancer Ovary

Essay

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By

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Allah

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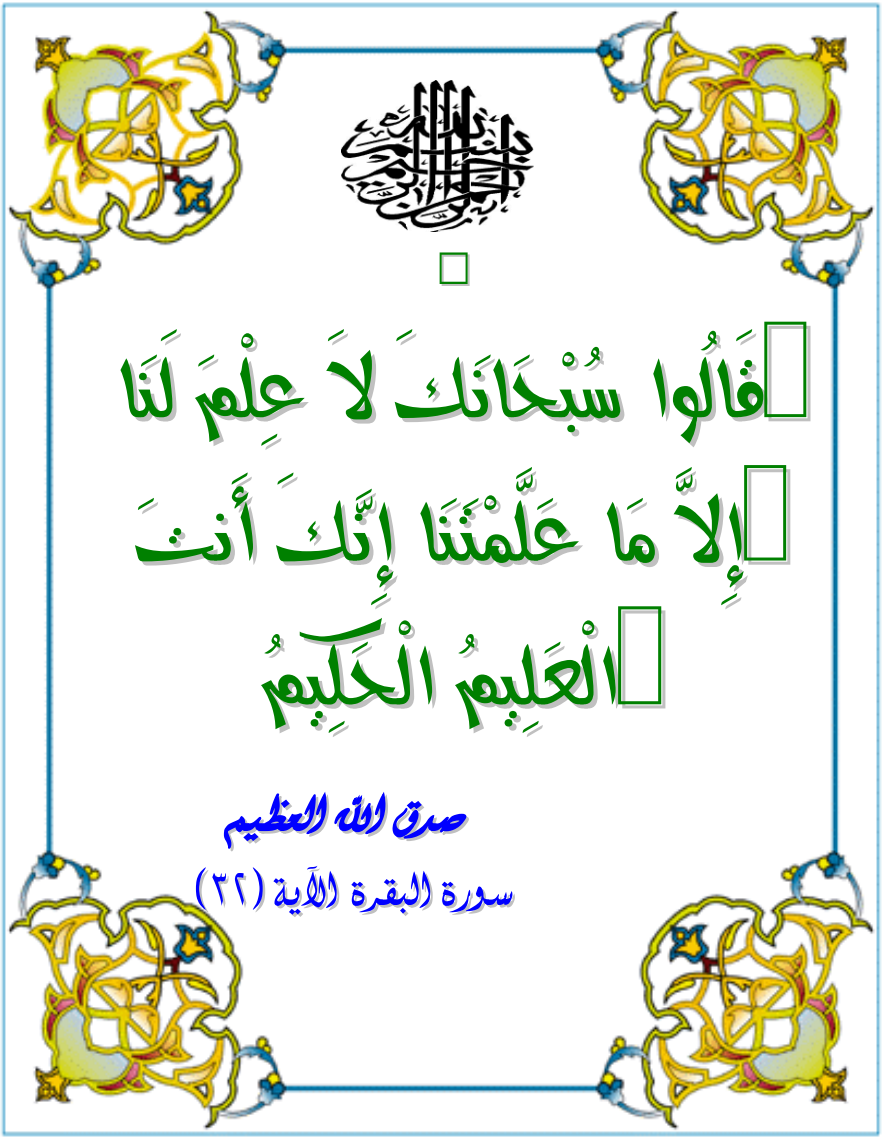

﴿قَالُوا سُبْحَانَكَ لاَ عِلْمَ لَنَا
إِلاَّ مَا عَلَّمْتَنَا إِنَّكَ أَنتَ
الْعَلِيمُ الْحَكِيمُ﴾

صدق الله العظيم

سورة البقرة الآية (٣٢)

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List of Abbreviations

Abb.	Meaning
AEs	Adverse events
AFP	Alpha-fetoprotein
BEV	Bevacizumab
BFGF	Basic fibroblast growth factor
BMI	Body mass index
CCC	Clear cell carcinoma
CDK	Cyclin-dependent kinase
CI	Confidence interval
CK7	Cytokeratin 7
CR	Complete remission
CREB	cAMP response element-binding protein
CSF	Colony stimulating factor
CT	Computerized tomography
CVC	Cancer Vaccine Collaborative
CWG	Cytokine Working Group
CXR	Chest X Ray
DCs	Dendritic cells
DFS	Disease free survival
DHFR	Dihydrofolate reductase
DOX	Doxorubicin
EC	Endometroid carcinoma
EGFR	Epidermal growth factor receptor
EORTC	European Organization for Research and Treatment of Cancer
EPIC	European Prospective Investigation into Cancer and Nutrition

Abb.	Meaning
EPIC	European prospective investigation into cancer and nutrition
ER	Estrogen receptor
FDA	Food and Drug Administration
FDG-PET/CT	Fluoro-D-glucose positron emission Tomography/Computerized tomography
GCIG	The Gynecologic Cancer Intergroup
GEM	Gemzar
GIP	Gastrointestinal perforation
GLUT-1	Glucose transporter 1
GOG	Gynecologic Oncology Group
HCG	Human chorionic gonadotropin
HD	High dose
HFSR	Hand foot skin reaction
HGSC	High-grade serous carcinomas
HRT	Hormone replacement therapy
Hs	Hours
I.V.	Intravenous
IARC	International Agency for Research on Cancer
IARC	International Agency for Research on Cancer
IGF 1	Insulin growth factor 1
IGFBP 1-7	Seven high-affinity binding proteins
IR	Insulin receptor
IU	International Unit
Kg	Kilogram
LC	Local control
LDH	Lactate dehydrogenase
LGSC	Low grade serous carcinoma

Abb.	Meaning
LND	Lymph node dissection
LRF	Locoregional failure
MAPK	Mitogen activated protein kinase
MC	Mucinous carcinoma
MMAE	Monomethyl auristain E
MMPI	Matrix metalloproteinase inhibitors
MRI	Magnetic resonance imaging
mTOR	Mammalian target of rapamycin
mTORC1	Mammalian target of rapamycin complex 1
NCCN	National Comprehensive cancer network
NSAIDS	Non-steroidal anti-inflammatory drugs
NWLCN	North west London Cancer Network
OCP	Oral contraceptive pills
ORR	Overall response rate
OS	Overall survival
P53	Protein 53
PARPI	Polyadenosine ribose pathway inhibitors
PDGF	Platelet derived growth factor
PI3K	Phosphoinositide 3-kinase
PIP2	Phosphatidylinositol-4,5-bisphosphate
PR	Progesteron receptor
PR	Partial remission
RECIST	Response Evaluation Criteria In Solid Tumors
RR	Relative risk
RT	Radiation therapy
S.C.	Subcutaneous
SAM	S-adenosylmethionine
SD	Stable disease

Abb.	Meaning
SEER	Surveillance, Epidemiology and End Results
SWOG	Southwest Oncology Group
TAA	Tumor-associated antigen
TILs	Tumor-infiltrating lymphocytes
TKIs	Tyrosin kinase inhibitors
TTP	Time to progression
UK	United kingdom
US	Ultrasound
VEGF	Vascular endothelial growth factor
VEGFR-1	Vascular endothelial growth factor-1
Vs.	Versus
WHO	World health organization
XIAP	X-linked inhibitor of apoptosis protein

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Introduction

Ovarian cancer is the fifth cause of cancer related death in women, the second most common gynecological cancer and the leading cause of death from gynecological malignancies. Although it may arise from all cell types composing the ovaries as primary tumors of epithelial, sex cord-stromal, or germ cell origin and metastatic tumors that frequently originate in the gastrointestinal tract, the epithelial carcinomas are by far the most common (85-90% of all ovarian cancer) **(Kurman et al., 2010).**

Risk factors include nulliparity, early menarche, late menopause, age and strong family history of breast and ovarian cancer. About 10 % to 15% of woman with ovarian cancer has genetic predispositions of BRCA1 and BRCA2 mutations **(Gayther et al., 2010).**

Ovarian cancer is one of the least detectible cancers because vague symptoms such as fatigue, abdominal swelling or discomfort, trouble eating or frequent urination. So early detection of cancer patients remains an important objective in the field because over 70% of patients are diagnosed at late stage disease, with dissemination of tumor implants throughout the peritoneal cavity **(Hennessy et al., 2009).**

Only 10-15% of these patients maintain a complete response to the initial therapy .The five-year survival of patients that present with late stage disease, which is the case for most patients, remains at < 30% with a mean survival of 39 months **(Cho et al., 2009).**

Treatment options and recommendations depend on several factors, including the type and stage of cancer, possible side effects, the patient's preferences and personal considerations, such as the woman's age, planning to have children and the sexual function **(Van Nagell et al., 2011).**

The current standard treatment for advanced ovarian cancer consists of cytoreductive (debulking) surgery, usually a bilateral salpingo-oophorectomy (removal of the ovaries and fallopian tubes) and hysterectomy are performed. The surgeon may also remove the omentum to determine whether the cancer has spread. Also remove lymph nodes, tissue samples, and fluid from the abdomen **(Safra et al., 2011).**

Chemotherapy as Paclitaxel combined with platinum-based regimen is the standard first-line chemotherapy used for all patients with ovarian cancer. Although clear cell type is categorized in indolent type, it is known to show relatively strong resistance to carboplatin and paclitaxel regimen and thus poor prognosis compared to serous adenocarcinoma, especially in advanced stages. Irinotecan plus cisplatin therapy may be effective for the clear cell adenocarcinoma **(Monk et al., 2010).**

Intraperitoneal chemotherapy possibly improve progression-free and overall survivals (PFS and OS). However, it has not been universally accepted for the toxic effects and intraperitoneal complications **(Pujade-Lauraine et al., 2010).**

Radiation treatment is not usually used to treat ovarian cancer, but it may be used to relieve side effects. Which depend on the dose and the area of the body being treated, but may include fatigue, mild skin reactions, upset stomach, and loose

bowel movements. Side effects of internal radiation therapy may include abdominal pain and bowel obstruction. Most side effects usually go away soon after treatment is finished **(Vencken et al., 2011).**

Recurrence is associated with incurable diseases in most cases. Thus, the main obstacle to an effective treatment is the failure of the initial chemotherapy to eradicate a sufficient number of tumor cells to prevent disease recurrence. In this context, deficiency in the apoptotic cascade among tumor cells is the key hallmark **(Vergote et al., 2010).**

Improved prognosis in ovarian carcinoma is related to the use of the new biological agents. One of the most investigated and promising molecular targeted drugs in ovarian cancer is **bevacizumab,** a monoclonal antibody directed against VEGF. A recent study demonstrated positive results of bevacizumab on progression-free survival in ovarian cancer patients. Two phase III trials have recently evaluated the role of bevacizumab in first-line chemotherapy as an adjunct to carboplatin and paclitaxel **(Katsumata et al., 2012)**. Other molecular target therapies include EGFR tyrosine kinas, HER2 receptor, PARP inhibitors .Multiple PARP inhibitors in development trials (Olaparib, Veliparib, Rucaparib, BMN 673, others). Trials combining PARP inhibitors with chemotherapy (**Yoshino et al., 2012).**

A phase III study of **farletuzumab** in combination with carboplatin and a taxane in patients with platinum-sensitive epithelial ovarian cancer in first relapse. The study did not meet the study's primary endpoint of progression-free survival (PFS).