Paclitaxel/Carboplatin versus Carboplatin in Patients with Epithelial Ovarian Cancer

and correlation to serum marker VEGF

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List of Abbreviations

ADL	Activities of daily living
AUC	Area under the curve
BRCA	Breast cancer gene
CI	Confidence Interval
CT	Computed Tomography
DFS	Disease Free Survival
ECOG	Eastern Cooperative Oncology Group
EOC	Epithelial Ovarian Carcinoma
EORTC	European Organization for Research and Treatment of Cancer
ER	Estrogen receptor gene
FIGO	International Federation of Gynecologists and Obstetricians
GOG	Gynecologic Oncology Group
HNF-1b	Hepatocyte nuclear factor – 1b gene
HNPCC	Hereditary Non-Polyposis Colorectal Cancer
HRT	Hormonal Replacement Therapy
ICON	International Collaborative Ovarian Neoplasm Trial
LMP	Tumors of Low Malignant Potential
MUC-1	Mucin – 1
NEMROCK	Kasr El Einy Centre of Clinical Oncology and Nuclear Medicine
OCP	Oral contraceptive pills
OR	Odds Ratio
OS	Overall Survival
PAC	Cisplatin – Doxorubicin – Cyclophosphamide regimen
PBSO	Prophylactic bilateral salpingo-oopherectomy
PCOS	Polycystic ovarian syndrome
PET	Positron Emission Tomography
PFS	Progression Free Survival
PPV	Positive Predictive Value

SLL	Second look laparotomy
SWOG	Southwest Oncology Group
TPN	Total parenteral nutrition
TVS	Trans-vaginal Ultrasonography
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organisation
WT-1	Wilm's tumour – 1 gene

Abstract

This study is a prospective non-randomized study including 50 patients with established diagnosis of epithelial ovarian carcinoma attending Kasr El Einy Centre of Clinical Oncology (NEMROCK) in the period from January 2006 to December 2007 inclusive.

After complete diagnosis and staging work up, the patients received either Paclitaxel 175 mg/m^2 followed by Carboplatin AUC 5 (Arm A) or single agent Carboplatin AUC 7 (Arm B) for 6 cycles provided adequate response occured after 3 cycles as assessed by CA 125 and CT scan.

At a median follow up period of 16.3 months, the median progression free survival was 10.8 months with a mean value of 23.18 months. About 60 % of patients showed no disease progression at 2 years. There was no statistically significant difference between the 2 arms in either the response rate or the progression free survival.

Serum Vascular Endothelial Growth Factor at baseline seems to have no prognostic value with no correlation to either disease stage or outcome.

Key words: Ovarian carcinoma, single agent carboplatin, AUC 7, VEGF.

Introduction

And

Aim of Work

Introduction:

Despite the fact that it is a highly curable disease if diagnosed early, cancer of the ovaries causes more mortality in women each year than all other gynecologic malignancies combined.

In the United States, ovarian cancer accounts for 4% of all cancer diagnoses and 5% of all cancer deaths. The lifetime risk of developing ovarian cancer is approximately 1.7%, although patients with a familial predisposition have a much higher lifetime risk, in the range of 10% to 40%.[1]
In Egypt, based on Gharbeya Population Cancer Registry, ovarian cancer represents around 3.7% of female cancer cases.[2]

Ovarian cancer is primarily a disease of postmenopausal women, with the large majority of cases occurring in women between 50 and 75 years old with a median age at diagnosis of 63 years. The incidence of ovarian cancer increases with age and peaks at a rate of 61.5 per 100,000 women in the 75–79 year old age group.[3]

There are distinct geographic variations in the incidence of ovarian cancer, with the highest rates found in the industrialized countries and the lowest rates seen in underdeveloped nations. Japan, with an incidence of only about 3.0 per 100,000 population, is a notable exception to this observation. It has been postulated that geographic variations in the incidence of ovarian cancer are related, in part, to differences in family size.[1]

During the past 30 years, survival has increased owing to improvement in diagnosis, surgery and chemotherapy. Despite these advances, most patients will die from the disease, and the overall 5-year survival is around 50%.[1]

Most patients require chemotherapy after initial surgery; and during the past 20 years, a large number of clinical trials have led to the adoption of the combination of carboplatin and paclitaxel as the international standard of care. This choice is based on

the results of sequential randomized controlled trials: from the synthesis of alkylating agents (chlorambucil and melphalan) in the 1950s; their use as single agents in the 1960s; the development of cisplatin and carboplatin in the 1970s and early 1980s, respectively; the controversies in the late 1980s about the addition of other drugs to platinum and whether or not cisplatin and carboplatin are of equal efficacy; through to the introduction of paclitaxel in the 1990s. For much of this time, issues of dosing and route of administration were hotly debated, and these questions have not been entirely resolved yet.[62]

Dose intensification has long been proposed as a means of overcoming drug resistance. There is some in-vitro evidence that platinum-resistant cell lines can be killed if drug concentrations are increased several folds. There have been 11 randomized studies on the effect of increasing platinum dose within the standard therapeutic range for ovarian cancer. Nine of the studies found no difference in outcome for patients assigned different doses of platinum, whereas two have shown a benefit for an increase in platinum dose intensity.[152-157]

The superiority of a platinum and paclitaxel combination regimen over single agent platinum remains the subject of debate in some quarters. Two randomized trials, ICON-3 and GOG-132, have suggested that single-agent platinum (carboplatin and cisplatin, respectively) is equivalent to combinations with paclitaxel. An unexplained observation when paclitaxel and carboplatin are given together is that there seems to be myeloprotection, with rather less thrombocytopenia than predicted. Consequently, one hypothesis put forward to explain the results of ICON-3 and GOG-132 that is partly borne out by experimental data is that the interaction between the two drugs could be antagonistic not only in bone-marrow stem cells but also in tumor cells; paclitaxel, perhaps through a cell kinetic effect, seems to abolish the effects of carboplatin.[125, 126]

Vascular endothelial growth factor (VEGF) is a major angiogenic factor that regulates multiple endothelial cell functions, including mitogenesis. Overexpression of VEGF is

associated with increased angiogenesis, growth, invasion, dissemination and metastasis in solid tumors.[162]

Overexpression of VEGF by ovarian cancer cells is a major mediator of angiogenesis in this tumor type and serum values may therefore serve as a prognostic tool. Kondo et al developed an Enzyme-Linked Immuno-Sorbant Assay (ELISA) for VEGF.[235]

Objectives and Aim of work:

The aim of this study is to compare the standard chemotherapy protocol for ovarian carcinoma (Paclitaxel / Carboplatin AUC 5) to single agent Carboplatin AUC 7 as regard the response rate, progression-free survival and relapse rate at 2 years; as well as prognostic value of different factors, namely: age, stage, grade, baseline CA-125 and serum VEGF at presentation.

Review Of Literature

CHAPTER I

Risk Factors and Genetics

Etiology:

Epithelial ovarian carcinoma is thought to arise from the surface epithelium of the ovary or from entrapped epithelial cells in inclusion cysts. There are several current hypotheses which attempt to explain the aetiology of ovarian cancer, such as the incessant ovulation hypothesis which suggests that cancers arise through repeated trauma to epithelial cells during ovulation and therefore factors which suppress ovulation will be protective. However, none of the hypotheses completely explain all the data from epidemiology, and there is a need for a greater understanding of the pathogenesis of ovarian cancer in order to develop new strategies for prevention.[4]

Genetic factors (inherited and somatic) as well as hormonal and environmental exposures all contribute to the development of ovarian cancer. Only 5% to 10% of patients with epithelial ovarian carcinoma likely have inherited a genetic predisposition to the disease; however, many studies have focused on these individuals in the hope of gathering additional insight into ovarian cancer biology, molecular oncogenesis, early detection, and treatment.

Risk factors and protective factors:

There is increasing evidence from case-controlled and cohort studies that several factors affect the risk of ovarian cancer.

It has been suggested that numerous dietary factors increase the risk of ovarian cancer, although the magnitude of the reported increase is relatively modest. In particular, galactose[5], animal fats and meat consumption (OR 1.63, 95% CI 1.25-2.12)[6] have been postulated to increase the risk; while a high-vegetable diet (OR 0.59, 95%CI

0.45-0.78)[6] and high consumption of olive oil (OR 0.80, 95%CI 0.65-0.99)[7] have been suggested to decrease the risk.

A single population-based cohort study has suggested that obesity may be a risk factor for ovarian cancer. It was reported that being in the upper tenth percentile for the body mass index (weight divided by height squared) increases the risk significantly, OR 1.7 (95% CI 1.1-2.7).[8]

Various environmental risk factors also have been suggested. Exposure to talc powder (hydrous magnesium trisilicate) has been reported in some studies to increase the risk of ovarian cancer, although other studies have failed to find an association. Talc is commonly used to dust the perineum, and it has been postulated that this talc may increase the risk of ovarian cancer by ascending the genital tract. This theory arose from observations that asbestos was associated with mesothelioma.[9] It was subsequently shown that particulate passage from the vagina to the ovary was possible.[10] Magnesium silicate particles, chemically similar to asbestos, have been seen in ovarian tumors[11], although a further study failed to confirm this unequivocally.[12] The theory has been supported by two US case-control studies[13, 14]. In the earlier study, the OR for ovarian cancer after genital exposure to talc was 1.5 (95% CI 1.0-2.1), while the 1999 study showed OR 1.6 (95% CI 1.18-2.15).

In contrast to the conflicting data on dietary and environmental factors, some clear associations have been drawn between certain hormonal and reproductive factors and the risk of developing ovarian cancer. The evidence is based on two main studies: the Wittermore review of 12 US case-control studies, involving 1771 cases and 7665 controls, investigating the epidemiology of ovarian cancer published in 1992 by the Collaborative Ovarian Cancer Group[15] and the American Nurses Cohort study that includes 121,700 US women who have been studied prospectively since 1976.[16]

Reproductive factors

Parity

The effects of parity have been studied more than any of the other known factors that affect the incidence of ovarian cancer. Two reports in particular showed the dramatic effect of increasing parity. Whittemore review shows the significant effect of a single term pregnancy; OR 0.47 (95% CI 0.40-0.56). This risk reduction is continued by further pregnancies so that after six term pregnancies the OR is reduced to 0.29 (95% CI 0.20-0.42).[15] In the American Nurses Cohort study as well, the effect of parity has been to reduce the risk of ovarian cancer; OR 0.84 (95% CI 0.77-0.91) for each pregnancy.[16]

Despite the hypothesis that multiple pregnancies may increase the risk of ovarian cancer, a review of the effects of multiple pregnancies on ovarian cancer, included results from eight studies concluded that in comparison to women who had carried singleton pregnancies, women who had had a twin pregnancy faced no increased risk of subsequently developing epithelial ovarian cancer.[17]

These studies show a highly significant effect of term pregnancies on the risk of ovarian cancer. What is less clear is the effect of pregnancies that fail to go to term, including miscarriages and terminations. A Danish case-control study found no relation between ovarian cancer and miscarriages (OR 0.93, 95% CI 0.72-1.20), induced abortions (OR 0.85, 95% CI 0.51-1.73) and ectopic pregnancies (OR 0.94, 95% CI 0.51-1.73).[18]

Breast-feeding:

The Whittemore review separated the effects of breast-feeding from pregnancy. A small protective effect from breast-feeding was demonstrated (OR 0.81, 95% CI 0.68-0.95).[15]

Early menarche and late menopause:

It has long been thought that early menarche and late menopause, i.e., a long menstrual life, are significant risk factors toward the development of ovarian cancer.