news

1.

Hormonal therapy in platinum resistance ovarian carcinoma: Do we have a chance?

Hormonal therapy for ovarian cancer has been evaluated through a number of hormonal agents. Tamoxifen has been the most examined agent in hormonal treatment of ovarian cancer. However, the mechanism of tumor suppression by tamoxifen is not known, yet. There are in vitro experiments on epithelial ovarian cancer cell lines with estrogen positive receptors that point to antiestrogen effects of tamoxifen.

Also, some studies point to relationship between the increase in incidence of ovarian malignancies and the rise in the serum gonadotropin concentrations. It has been suggested that gonadotropins are also involved in the development of ovarian tumors.

Continuous stimulation of the pituitary by chronic administration of gonadotropin-releasing hormone (GnRH) agonists, such as goserelin, leads to suppression of LH and gonadal steroid production. Furthermore, treatment of patients with LH-RH, resulting in reduced gonadotropin concentrations has been associated with a 17% response rate in patients with advanced disease.

Hasan and colleagues conducted a nonrandomized phase II evaluation of endocrine therapy combined with tamoxifen and goserelin in patients with advanced ovarian cancer that had recurred after chemotherapy.

In total, 26 patients entered the study, of which 17 had platinum-resistant disease. The median age was 63 years and enrolled patients had received a median of three chemotherapy regimens before trial entry. Patients were given oral tamoxifen 20 mg twice daily on a continuous basis and subcutaneous goserelin 3.6 mg once a month until disease progression. Using the definition of endocrine response that included patients with stable disease (SD) of 6 months or greater, the overall response rate (clinical benefit rate) was 50%. This included one complete response (CR) (3.8%), two partial responses (PR) (7.7%), and 10 patients with SD (38.5%). The median progression-free interval (PFI) was 4 months (95% CI 2.4-9.6) while the median overall survival (OS) was 13.6 months (95% CI 5.5-30.6). Four patients received treatment for more than 2 years (range 1-31) and one of them is still on treatment. In none of the four patients was there any evidence of recurrent or cumulative treatment related toxicity. Treatment-limiting toxicity was not seen in any of the study population. Endocrine data demonstrated a marked suppression of luteinising hormone (LH) and follicle-stimulating hormone (FSH) to less than 4% of baseline values. No consistent correlation could be established between LH/FSH suppression and tumor response. Likewise, no relationship was observed between inhibin A/B and pro-alpha C levels and tumor response. Inhibin is unlikely to be a useful surrogate marker for response in locally advanced or metastatic ovarian cancer. Combination endocrine therapy with tamoxifen and goserelin is an active regimen in platinum-resistant ovarian cancer patients. Hormonal therapy is advantageous in its relative lack of toxicity, ease of administration and tolerability, thus making it suitable for patients with heavily pretreated disease, compromised bone marrow function and other comorbid conditions that contraindicate cytotoxic therapy as well as in patients with indolent disease. Nevertheless, prospective randomized studies need to be performed to confirm the superiority of this regimen.

REFERENCE

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2.

Long term follow-up of patients treated for Helicobacter pylori infection

Helicobacter pylori infection induces progressive inflammatory changes in the gastric mucosa, which may lead to gastric cancer and has been categorized as a class I carcinogen. This study is a result of the cooperation of authors from Cali, Colombia and from New Orleans, USA, and was carried out on volunteers as randomized placebo controlled study in a high-risk gastric cancer area of Colombia. A cohort of 795 adults with preneoplastic gastric lesions was randomized to receive anti-*H. pylori* treatment (two weeks amoxicillin, metronidazole, and bismuth subsalicylate) or placebo (antioxidants-β-carotene and ascorbic acid). Subjects assigned to the anti- *H. pylori* treatment who tested positive for *H. pylori* at 36 months were re-treated for 14 days (amoxicillin, clarithromycin, and either omeprazole or lansoprazole). At the end of six years of intervention, those who did not receive anti-*H. pylori* treatment were offered it. Gastric biopsies were obtained at baseline, and at 3, 6, and 12 years. A total of 638 (80.25%) patients were biopsied on three or more occasions. A histopathology score, based on the extent of gastric atrophy, type and extension of intestinal metaplasia and grade of dysplasia, was utilized to document changes in gastric lesions.

Among patients that received anti- *H. pylori* therapy at baseline (n = 394), eradication rates at 3, 6, and 12 years were 51% (171/336), 75% (239/320), and 51% (153/300), respectively. The clearance rate at 12 years among patients that did not receive anti- *H. pylori* therapy at baseline but were offered and received it at the six-year mark was 47% (84/180). The estimate spontaneous clearance rate was 2.9% per year; on the other hand, the reinfection/recrudescence rate was calculated 5.4% per year. There was a strong and significant effect of age on spontaneous clearance and reinfection/recrudescence rates. Subjects younger than 50 years at baseline had smaller spontaneous clearance rates and larger reinfection/recrudescence rates than patients over 50 years old.

The progressive atrophy and later intestinal metaplasia that develops after many years of *H. pylori* infection might at first be thought to be an irreversible process. The anti-oxidant treatment had no effect, whereas *H. pylori* eradication therapy significantly improved histology at 12 years. This improvement was proportional to the square of the duration of time that the patient was free from *H. pylori* infection. The patient who cleared the infection had declining histopathology scores as a function of the square of time. At six years, the score for those subjects was 0.13 less than baseline, while at 12 years the score was 0.59 less than baseline. Those subjects who have never been treated and remained infected had an increase in score of 0.18 at 12 years. Treated patients (at any point) who were still infected at 12 years (treatment failure) had a decrease in score of 0.19. It may be a bit surprising that are approximately the equal numbers of diagnosed new cases of gastric carcinoma in the treated and control groups. There were nine new gastric carcinoma cases during the 12 years of follow up: five in the *H. pylori* treatment group (four had dysplasia and one had intestinal metaplasia at baseline) and four in the non-treated group (one had dysplasia

and three had intestinal metaplasia at baseline).

In this 12-year study, authors confirmed previous observations regarding regression of atrophy and intestinal metaplasia after the successful eradication of *H. pylori*. Especially the regression of intestinal metaplasia may be a long-term process, taking many years after the eradication of *H. pylori*. There were no statistically significant changes in dysplasia but there was a trend towards more regression and less progression among patients that remained consistently negative for infection.

The authors concluded that prevention of gastric cancer by eradiation of *H. pylori* is a viable option but that very prolonged studies are needed to clearly show the benefit, because the greatest beneficial effects might not be evident in the first 3-6 years of observation. The message is clear that patients with pre-neoplastic gastric lesions should be treated and cured of their *H. pylori* infection.

Four months after accepting the publication the significance of this study was confirmed by the decision of the Nobel Assembly at Karolinska Institutet to award the Nobel Prize in Physiology or Medicine for 2005 jointly to Barry Marshall and Robin Warren for their discovery of "the bacterium *Helicobacter pylori* and its role in gastritis and peptic ulcer disease".

REFERENCE

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