Exemestane experience in breast cancer treatment

P E Lønning, R Paridaens, Beat Thürlimann, G Piscitelli & E Di Salle

Exemestane is a very potent, orally active, selective and long-lasting steroidal irreversible inhibitor of aromatase. It is 150 times more potent than aminoglutethimide (AG) in inhibiting human placental aromatase (Ki of 4.3 and 671 nM, respectively). The compound is presently under phase III evaluation in Europe and the U.S.A. for the treatment of postmenopausal advanced breast cancer (ABC). Clinical pharmacology studies have been carried out with single doses ranging from 0.5 to 800 mg and repeated doses of up to 600 mg a day, in 132 postmenopausal healthy volunteers and in 185 postmenopausal women with ABC. Results obtained using a very specific and sensitive analytical method (high performance liquid chromatography-radioimmunoassay; HPLC-RIA) indicated that exemestane is extremely effective in inhibiting plasma estrogens levels. Estrogen inhibition is clearly evident at 5 mg a day and maximal suppression for E2, E1 and E1S (>85%, >90% and >90%, respectively) is obtained at 10-25 mg a day. Data from non-controlled phase II studies involving more than 400 patients indicated a clear anti-tumour activity in postmenopausal ABC patients failing multiple hormonal treatments. In 62 patients progressing on AG (> or = 500 mg a day) exemestane treatment resulted in an objective response rate of approximately 24%; disease stabilization > or = 24 weeks was observed in an additional 24% of cases. With regard to safety, although daily doses up to 600 mg were administered, the maximal tolerated dose was not achieved; reported symptoms were mainly related to the pharmacological action of the compound and were usually mild to moderate in severity, resulting in the discontinuation of therapy in less than 3% of cases. In conclusion, the available results suggest that exemestane treatment is associated with minimal toxicity, and may be of significant benefit for ABC women who have exhausted conventional therapy.