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Ribonucleotide Reductase Inhibition in the Treatment of Advanced Prostate Cancer: an Experimental Approach with Hydroxyurea and Gallium Nitrate in 20 Patients

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TREATMENT OF hormone-resistant prostate cancer is associated with poor outcome, with doxorubicin being probably the most effective chemotherapeutic agent, but unable to modify the life expectancy of these patients [1]. It is, therefore, necessary to study new therapies in this setting. It is known that tumour cells are more sensitive to iron depletion than normal tissue [2–5]. The major target of iron depletion in higher eukaryotic cells is the ribonucleotide reductase, an enzyme catalysing conversion of ribonucleotides to deoxyribonucleotides. The ribonucleotide reductase is composed of two subunits: the M1 subunit, inhibited by hydroxyurea (HU); and the M2 subunit, inhibited by gallium nitrate (GN) which replaces iron in its core. Both drugs directly inhibit DNA synthesis as a result of the ribonucleotide reductase inhibition and, particularly, the cytotoxic effect of HU is cell-cycle-specific for the S phase. HU has been previously tested in 27 patients affected by prostate cancer, with objective remissions in 15% [6, 7], while GN has been found to be active in bladder cancer [8]. Moreover, HU and GN have been found to have a marked anticancer activity *in vitro*, with inhibition of leukaemic cell growth, probably with a synergistic mechanism [9]. Based on these findings, we decided to study the combination of HU and GN in a phase II study to assess its efficacy and toxicity in advanced hormone-resistant prostate cancer.

Since August 1993, at the Division of Medical Oncology and AIDS of the Centro di Riferimento Oncologico of Aviano, Italy, patients with hormone-resistant prostate cancer have entered this phase II study. Eligibility criteria included (i) histologically confirmed prostate adenocarcinoma; (ii) performance status more than 60% according to Karnofsky; (iii) advanced disease refractory to all conventional, in particular hormonal, modalities of treatment; (iv) life expectancy >3 months; (v) white blood cells > 4000/mm^3; (vi) platelets > 100 000/mm^3; (vii) total bilirubin < 1.5 mg/dl; (viii) SGOT < 120 UI/l; (ix) albumin > 3 g/dl and (x) creatinine < 1.5 mg/dl. Previous palliative radiotherapy on bone metastases did not preclude patients' eligibility. Parameters of evaluation were: prostate specific antigen (PSA); all patients started therapy with high PSA levels, i.e. with more than > 4 ng/ml, bone scan and skeletal X-ray in case of bone metastases. Objective responses were evaluated according to the criteria of National Prostate Cancer Project [10] including PSA value.

The treatment plan consisted of GN at a dose of 700 mg/m^2 i.v. (intravenous) on day 1 and HU 500 mg orally every 8 h on days 2–5 every 21 days, for at least two cycles. Toxicity and response were assessed after each cycle. At least two cycles had to be administered in order for patients to be considered evaluable for treatment.

From August 1993 to April 1994, 20 patients entered the trial. All were affected by stage D prostate cancer, median age was 78 years (range 57–85 years). 16 of the 20 (80%) patients were pretreated with hormone therapy, and 4 (20%) with hormone chemotherapy. Overall, 73 cycles were administered, with a median number of 4 (range 2–8). Toxicity, according to WHO, was mild, with sideropenic anaemia being the most frequent toxic effect.

The response rate was as follows: partial response 2/20 (10%) 95% CI (confidence interval): 3–30%, no change 4/20 (20%) (95% CI: 8–42%), progressive disease 14/20 (70%) (95% CI: 48–85%). The two partial responses, defined as a decrease of PSA value >25%, lasted 3 and 8+ months.

This phase II study shows that the combination of HU and GN in hormone-resistant prostate cancer has no relevant antitumour activity, at least at the doses and schedule employed. The toxicity was mild. Since this treatment was theoretically designed for tumours resistant to conventional therapy, its failure in advanced hormone-resistant prostate cancer does not preclude its potential activity in other solid tumours.

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