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Meeting abstract

Epigenetic therapy with hydralazine and valproate associated to cisplatin chemoradiation in FIGO stage IIIB. A phase II study

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Background

Standard chemoradiation with cisplatin has improved the results of treatment, however, newer therapeutical modalities are needed. DNA demethylating and histone deacetylase inhibitors have shown radiosensitizing effects as well as potentiation of chemotherapy drugs. This study was set to evaluate hydralazine and valproate as epigenetic therapy added to chemoradiation with cisplatin in cervical cancer.

Materials and methods

Eligibility criteria included untreated disease, histological diagnosis and adequate bone marrow, hepatic and liver function. Patients were typed for acetylator phenotype and then oral hydralazine at 182 mg/day or 83 mg/day for rapid and slow-acetylators respectively. Oral magnesium valproate was used at 30 mg/Kg/day. Treatment started 7 days before commencing chemoradiation. Chemoradiation consisted on EBRT 50 Gy in 2G fractions plus cisplatin at 40 mg/m2 weekly × 6. Brachytherapy was scheduled after EBRT. Response, toxicity and survival were evaluated as well as the biological effects of hydralazine and valproate in blood and primary tumor samples.

Results

Twenty one patients were included. Mean age was 50.4 years (range: 28–69 y). Overall, 85% of patients completed both phases, external beam and intracavitary therapy. Three patients did not receive brachytherapy: two abandoned treatment during EBRT and one died after the first cycle of chemotherapy. Mean + SD dose administered to point A was 84.6 + 2.2 (range: 79.6 – 87 for point A). Median number of cisplatin cycles administered was five (range 1–6). The 18 patientes evaluable for response achieved complete clinical response after EBRT. The most frequent grade 3/4 hematological toxicity was neutropenia (45%), followed by thrombocytopenia (10%) and anemia (10%). Non-hematological toxicity was mild in most of cases. Three out of 18 cases have relapsed (16.6%): one local, one had local/systemic relapse and one systemic, at a median follow-up of 11 months (range: 1 – 13.4 m). The hydralazine/valproate-induced changes in the expression of genes analyzed by microarrays will be presented in the meeting.

Conclusion

Epigenetic therapy with hydralazine and valproate associated to chemoradiation in cervical cancer is well-tolerated

and seems effective as all evaluable patients achieved clinical complete response during the external radiation.