CAPACITIVE HYPERTHERMIA WITH CONFORMAL RADIOTHERAPY FOR TREATING GLIOBLASTOMA: BIOLOGIC REASONS AND CLINICAL RESULTS

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Par A: Biological Reasons for using Hyperthermia with radiotherapy

Glioblastomas multiforme (GBL) and Astrocytomas grade III-IV are the most aggressive forms of primary brain tumors in adult. These patients are still beyond cure despite extensive surgery, improved radiotherapy, and combination chemotherapy. The median survival time after surgical excision is at best only about 14-15 months. The therapies in clinical use are not sufficient optimal and every effort should be made to find new therapy schema. Hyperthermia has demonstrated to be successfully used in association with radiotherapy and chemotherapy for different reasons.
Glioblastomas not dissimilarly than other solid tumours tend to have a more acidic and hypoxic microenvironment than normal tissue. This hostile microenvironment results from a disparity between oxygen supply and demand of the tumor tissue. Overcoming hypoxia tumor induces a new vascular supply. This new vasculature is however inefficient and chaotic. It perpetuates the factors that have stimulated its induction. The acidic and hypoxic microenvironments are detrimental for radiotherapy, in fact hypoxic tumors are more radioresistant, on the contrary hyperthermia exerts its biological effects easily in acidic and hypoxic state. Furthermore hyperthermia has clearly demonstrated to inhibit angiogenesis in vitro and in vivo down modulating endothelial proliferation induced by Vascular Endothelial Growth Factor (VEGF) by activating Plasminogen Activator Inhibitor I – dependent mechanism (PAI-I). Glioblastomas seem also sensible to the cytotoxic effect of heat, has reported by Mondovi and to increase its effect in association with CCNU and BCNU. Studies by Shem and Dahl have also reported that the association of BCNU with hypertonic glucose can increase further the heat effect. For these reasons Hyperthermia associated with radiotherapy and chemotherapy show solid biological reasons for treating GBL a tumor with a great dismal prognosis.

Part B: Clinical preliminary Results

Methods and materials
Thirteen patients (4 male 9 female; median age 37) with low and high grade astrocytoma underwent combined therapy (CT+CFRT+HT) according to the following schedule: two hours before first session of HT the patient assumed 120 mg BCN then HT was applied; a cycle of HT consisted with at least 5 application every 48 Hrs. Thirty minutes before each HT session 4 mg of dexamethasone was delivered IV associated to an hypertonic 10% glucose solution lasting the whole session.
All patients were treated with standard dose of anticonvulsant to avoid seizures.
Results
The survival curves of the HT group and the standard CFRT group were compared according to Kaplan-Meyer method and log Rank test.
The whole HT group showed a better survival (median survival 14 vs 42 Months: p=0.003) with statistical significance; a second comparison was attempted excluding patients other than GBL; even in this case the results are in favour of HT group (Median survival 14 vs 28 months p=0.04)
No serious side effect due to the HT was scored showing a low toxicity rate;
This preliminary study shows a good feasibility and tolerance of the schedule together with acceptable results: in a close future new drugs and slightly different sequence will be tested and a randomised study will be taken in consideration soon.