Peritumoral edema treatment

The use of corticosteroids to treat cerebral edema in brain tumor patients dates back to case reports by Ingraham and Matson in 1952 [1].

A few years later, a new corticosteroid with comparatively low mineralocorticoid properties and high glucocorticoid potency named dexamethasone was first synthesized [2].

In the early 1960s, Galichich and colleagues published their experience with dexamethasone in brain tumor patients [3].

Ever since, dexamethasone has been the standard corticosteroid used to treat vasogenic cerebral edema in brain tumor patients. Despite its widespread use, there are few prospective studies available to guide the optimal dosing and use of dexamethasone [4].

Dexamethasone (DEXA) is widely used in the management of peritumoral edema. DEXA, however, has many systemic side-effects, and may interact negatively with glioma therapy. Progesterone (PROG), on the other hand, is a well-tolerated and readily accessible antiinflammatory and anti-edema agent with potent neuroprotective properties.

Cheng et al., investigated if PROG can serve as a viable alternative to DEXA in the management of peri-tumoral brain edema.

They used an orthotopic C6 glioblastoma model with male Sprague Dawley rats. Tumor grafts were allowed to grow for 14 days prior to drug treatment with (i) DEXA 1mg/kg, (ii) PROG 10mg/kg or (iii) PROG 20 mg/kg for five consecutive days. Overall animal survival and neurologic functions were evaluated. Mechanistic studies on blood brain barrier (BBB) permeability and angiogenic responses were performed on the ex vivo tumor grafts.

They found that all drug treatments prolonged overall survival to different extents. PROG 10mg led to significantly longer survival, and better preservation of neurologic functions and body weight. BBB permeability was better preserved with PROG 10mg than DEXA possibly through the downregulation of MMP-9 and AQP-4 expressions; anti-angiogenic responses were also observed in the PROG group.

This proof-of-concept pilot study provides novel information on the use of PROG as a corticosteroids-sparing agent in brain tumor management. Further translational and clinical studies are warranted [5].

The Response Assessment in NeuroOncology (RANO) Working Group has developed consensus recommendations for endpoints evaluating corticosteroid use in clinical trials in both adults and children with brain tumors.

Responders are defined as patients with a 50% reduction in total daily corticosteroid dose compared with baseline or reduction of the total daily dose to ≤2 mg of dexamethasone (or equivalent dose of other corticosteroid); baseline dose must be at least 4 mg of dexamethasone daily (or equivalent dose of other corticosteroids) for at least one week. Patients must have stable or improved Neurologic Assessment in Neuro-Oncology (NANO) score or Karnofsky performance status score or Eastern

Cooperative Oncology Group (ECOG) (Lansky score for children age <16 y), and an improved score on a relevant clinical outcome assessment tool. These criteria must be sustained for at least 4 weeks after baseline assessment to be considered a response, and are confirmed 4 weeks after that (ie, 8 wk after baseline assessment) to be considered a sustained response.

This RANO proposal for corticosteroid use endpoints in neuro-oncology clinical trials may need to be refined and will require prospective validation in clinical studies [6].

1)
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