Effect of Bevacizumab and Everolimus for the treatment of Vestibular Schwannomas in patients with Neurofibromatosis Type 2

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This work was supported by the DDMoRe project (www.ddmore.eu)

Context

- Vestibular schwannomas (VS) are benign slow-growing tumors that touch the Schwan cells of the vestibular nerve and lead to hearing loss.
- Choice of surgery depends on the balance between benefits and risk as hearing and facial function can be definitely lost during the procedure.
- Antiangiogenic compounds are more and more used to treat VS but no standard dose level nor schedule exists.
- The main objectives of this work are to evaluate and compare the efficiency of bevacizumab and everolimus for the treatment of VS.

Tumor dynamic modeling

Data collection

- Data analysis included 22 patients with Neurofibromatosis Type 2 (NF2):
  - Bevacizumab 5 mg/kg Q2W (n=13)
  - Everolimus 10 mg QD (n=7)
- Both drugs at distinct periods (n=2)
- Tumors are classified into 4 stages according to their size that display a high variability.

Mechanism-based model

- Tumor size (P) is described by a Simeoni model where proliferation and cell death are depending on VEGF levels.
- Bevacizumab and VEGF concentrations in nM are simulated from a published TMD model. The drug reduces VEGF levels and its effects.
- Everolimus reduces VEGF synthesis through mTORC1 inhibition.

Model evaluation

Parameter estimates

- All parameters (Ka, λ5, P, Kdav, IC50, KS) were precisely estimated (rmse% < 50%).
- Cell death (Kdav) is 4 times higher with bevacizumab than everolimus.
- Growth becomes linear when tumor reach the size of 7.5 cm³ (P/λ0).
- During linear phase, growth rate is 0.3 cm³ per month.

Individual fits

Model evaluation

- Visual predictive check with the predictions and variability, comparison between observed tumor size dynamics (lines: 5th, 50th and 95th percentiles, ) and the 95% confidence intervals (blue and red areas) calculated from simulated data.

Conclusion

- We develop a mechanism-based mixed-effects model for the analysis of the dynamic of tumor volume of vestibular schwannomas treated with bevacizumab or everolimus.
- Our model confirms the roles of the vascular endothelial growth factor (VEGF) on the proliferation and survival of Schwann cells.
- Tumor shrinkage is more important with bevacizumab than everolimus as this latter activates a secondary pathway which increases tumor growth.

Simulations

Simulated tumor dynamics for 3 doses and a control group (no treated patients) stratified by compounds: bevacizumab and everolimus. For each treated group, a 3 years treatment is given after 3 years of growth.

- Tumor shrinkage through bevacizumab seems to be dose-dependent.
- A higher dose of everolimus does not improve tumor shrinkage and worsen the rebound after the end of the treatment.

References: