Clinical Care Protocol to use selumetinib as a treatment for inoperable plexiform neurofibromas - a proposal

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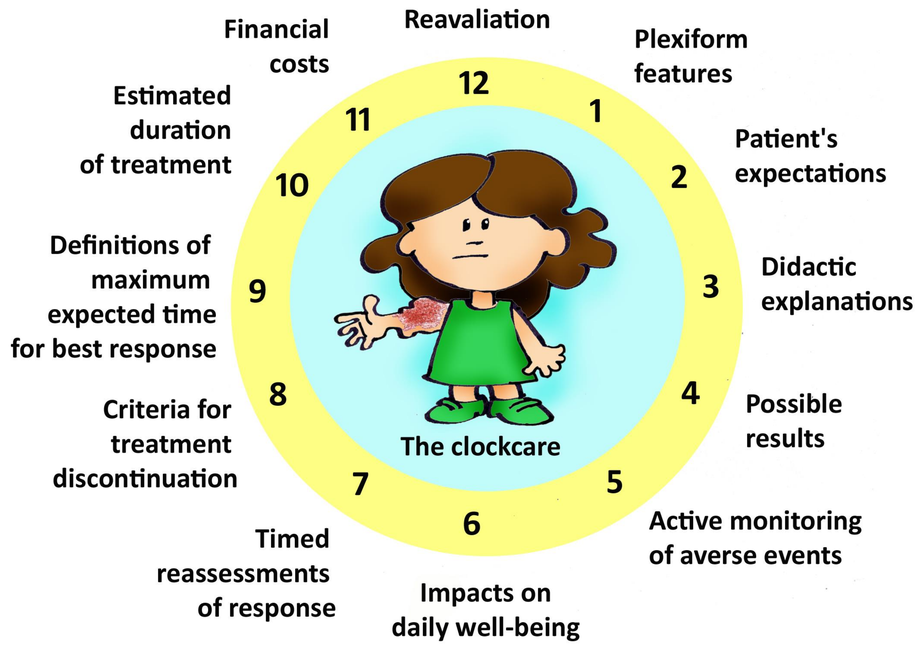
Background: Children with neurofibromatosis type 1 (NF1) may present with symptomatic and inoperable plexiform neurofibromas (PN). The MEK inhibitor selumetinib (SEL) has been FDA approved as an option in that context. The pivotal trial (Gross et al. 2020) results suggest a moderate (level 3) Magnitude of Clinical Benefit on the ESMO scale (ESMO-MCBS v1.1, 2020), through the evaluation form used for single-arm studies in orphan diseases when primary outcome is a surrogate such as response rate. The evidence, though, is of very low methodological quality, according to GRADE (Guyatt GH et al. 2011). Moreover, SEL's impact in patient-centered outcomes, such as overall survival, symptom control or quality of life (QoL), is uncertain. Evidence so far suggests that treatment might have to be continuous for a sustainable response. But, due to the lack of robust evidence on efficacy and safety of long term use of SEL in children, optimal treatment duration is unclear, atop possible effects of treatment discontinuation. Estimated direct financial costs of SEL seems high and it might not be cost-effective. This uncertainty around the real magnitude of net clinical benefit of SEL suggests that it should only be offered to patients in a careful informed-decision process, supported by care protocols.

Methods: Our group is developing a care protocol, including the following aspects (Figure 1 – The "clockcare"): 1) PN's features (location, volume, progression, symptoms, complications); 2) patient's expectations with treatment (symptom control, volume reduction, cosmetic improvement, complication avoidance, pain control); 3) thorough didactic explanations to patients of the best available evidence, with the use of NF1-appropriate patient decision aids (including illustrated age-adjusted tools); 4) realistic estimations of possible results, updated during treatment; 5) active monitoring of anticipated adverse events; 6) impacts of SEL on patient's daily well-being (objective measures of QoL); 7) timed reassessments of response, with defined clinical, imaging and laboratorial criteria; 8) clear criteria for treatment discontinuation; 9) definitions of maximum expected time for best response; 10) estimated duration of treatment; and 11) care-related patient's financial costs; 12) Protocol of reavaliations.



Conclusions: The systematic follow up of patients with SEL treatment for inoperable and complicated PN will generate real-world evidence on the actual clinical benefit of SEL to better inform patient's decisions.

Gross AM et al. N Engl J Med. 2020;382(15):1430-1442; ESMO-MCBS v1.1, EVALUATION FORM 3, 2020; Guyatt GH et al. J Clin Epidemiol. 2011;64(4):407-415; Institute of Medicine (US); Olsen LA et al. National Academies Press (US); 2011; Holmes-Rovner, M. Health Expect. 2007 Jun; 10(2): 103–107.

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