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Actinomycin D shortage in the Brazilian market: new challenges for successful treatment of gestational trophoblastic neoplasia

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Actinomycin D (Act-D) is the backbone of treatment regimens of highly curable tumors such as gestational trophoblastic neoplasia (GTN) and Wilms Tumor in children [1,2]. For example, in GTN, Act-D can be considered for first-line treatment as single-agent in low-risk and in combination for high-risk patients. For those with low-risk GTN, if not used in front-line, Act-D is used as rescue therapy after methotrexate (MTX) failure [1]. This leads to almost a 100% of cure among women with GTN with great tolerability (most common adverse events are mild nausea and alopecia), even in spread disease. In many instances there are no good substitute for Act-D.

In Brazil, every state has a reference center with GTN management expertise. Our guidelines at the Brazilian National Cancer Institute (NCI) are no different from many international guidelines and recommend to use MTX as first-line regimen for low-risk GTN patients, reserving Act-D to MTX resistant GTN, and for high-risk GTN or relapse disease, etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine (EMA-CO) is the regime of choice, using Act-D as one of the drugs [1].

Since 2013, Brazilian doctors are facing obstacles to treat tumors that need Act-D. The pharmaceutical companies decided no longer to market this cheap drug in our country due to goals that go beyond our knowledge. In the meanwhile, the government decided to import it from the Asian market and distribute it to public clinics/hospitals.

In January 2019, doctors from the gynecologic oncology department received a communication saying that there was no Act-D to treat patients with resistant/relapsed GTN. This is the second time that happens at the Brazilian NCI. In the first (2015), patients were treated with carboplatin (area under the curve 6 every 21 days) after MTX resistant GTN based in a single report from United Kingdom [3]. However, myelosuppression is a significant toxicity in patients receiving carboplatin, leading to treatment delays [3]. Other options in this setting may be etoposide as single agent or even multiagent regimen without Act-D (as EMA-CO). Nevertheless, patients with GTN are young and concerns about second malignancies have led us not to consider the early exposition to etoposide a good option in this scenario. How can we face this shortage again since we are responsible for the greatest amount of GTN treatment in our state? We should highlight that GTN mainly arrives from molar pregnancy, and as in Brazil we expected an incidence of molar pregnancy 5 to 10 times higher than in US and Europe, this may be a public health problem for our Brazilian women [4].

In December 2018, the Brazilian Ministry of Health decided not to import Act-D anymore and let at discretion of the local institutions to carry out this process. The government would pay these institutions, however, the costs of importing the drug (around US$ 1,400.00/month) is 4 times higher than the government pays per patient (around US$ 464.00/month) with the regime of 1.25 mg/m^2 every two weeks [5]. If it is difficult for relatively large institution as ours, what can we expect about hospitals in the poorest regions of Brazil, such as in the north and northeast? But this shortage does not affect only the Brazilian public health system. In private clinics, health insurance does not cover the import costs. In this case, patients need to pay not only for importation but also for the administration costs.

Important discoveries have been made in the treatment of GTN. One of them is the knowledge that this disease has a high expression of programmed death-ligand 1 (PD-L1) and immunotherapy could be active for these patients. In one study it was performed PD-L1 immunohistochemistry on 30 choriocarcinoma cases, 73% of which showed intense PD-L1 immunoreactivity in syncytiotrophoblasts [6]; in other it was demonstrated ubiquitous PD-L1 expression in 20 choriocarcinoma, suggesting a role for checkpoint inhibition in this so aggressive form of GTN [7]. There are some data about checkpoint inhibitors (CPi) in GTN. One case report with excellent serological response to pembrolizumab in a woman with chemoresistant metastatic choriocarcinoma was reported in the *Journal of Clinical Oncology* [8]. This patient was treated with 2 regimens of chemotherapy and relapsed. After exposure to pembrolizumab this patient was with no evidence of disease. In another correspondence article published in *Lancet Oncology* [9], four patients considered to be chemoresistant at the Charring Cross Hospital were treated with pembrolizumab: 3 of them achieved a complete and sustained remission. At the European Society for Medical Oncology (ESMO) 2018 it was presented the awaited results of TROPHIMMUN trial in GTN: a 2-cohort phase II trial in chemo-resistant patients that are being treated with avelumab. It was presented only the cohort of low-risk at this time [10]. Six patients were included and 3 patients achieved complete remission. The recruitment is still ongoing in this low-risk cohort (up to 15 patients) and the high-risk cohort will be presented in the near future. It is important to note that CPi are not without toxicities and some of them could be life threatening such as pneumonitis, hepatitis and myocarditis. Another experimental treatment was done with anti-endoglin antibodies; in a case published by group of the New England Trophoblastic Disease Center, one patient who had relapsed after single- and multiagent chemotherapy had a durable remission when combined to bevacizumab [11].

These are great discoveries but they also alert us about the cost-effectiveness of drugs, especially in low and low-middle income countries. Act-D is a cheap and well tolerable strategy in treatment of low-risk GTN or after MTX failure. Also, for those patients with high-risk GTN or relapse disease, Act-D is used in salvage therapy with combination regimes such as EMA-CO and etoposide and cisplatin with etoposide, methotrexate, and dactinomycin (EP-EMA). Because GTN is a highly curable disease with cheap drugs with known, less common and manageable toxicities, and adding this information to the fact that it is a rare disease, it will be difficult to find a substitute of Act-D in the near future. Looking into clinicaltrials.gov website using the term “gestational trophoblastic neoplasia” approximately 75 trials were found. Only 2 of them are recruiting patients and seeking for new therapeutic strategies: one is the avelumab trial described previously (NCT03135769) and the other is looking for the efficacy of carboplatin/cisplatin and paclitaxel in front-line for patients with high-risk disease (NCT02639650).

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The Brazilian societies and associations involved in the treatment of these patients are already mobilizing to restore the Act-D in the country's market. The Brazilian NCI began the process of importing the Act-D to the local patients, which can take about 4–6 months and will be covered by its own resources. Until then, a difficult scenario is drawn. The shared decision has become more difficult and, unfortunately, what should be a curable disease can become a tortuous path to successful treatment.

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