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Case Report

Case Report: Automated Compounding of Everolimus Tablets for a Pediatric Glioma

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Abstract:

This case report highlights the challenges faced in administering oral anticancer therapies to pediatric patients unable to swallow commercially available dosage forms. Using an automated extemporaneous compounding system, we produced an oral semisolid formulation with the necessary dose to be able to manage the treatment for a 7-year-old girl with diffuse intrinsic pontine glioma (DIPG), H3-K27M-mutant, mTOR mutant, WHO grade IV.

Keywords: anticancer therapy; extemporaneous compounding

Introduction

The increasing use of oral anticancer therapies offers a seemingly simplified alternative to intravenous chemotherapy but poses unique challenges, particularly for pediatric populations who may have difficulties swallowing solid dosage forms. Many oral cancer drugs are not available in formulations suitable for younger patients such as solutions, suspensions and granules, necessitating the exploration of compounding safe and effective alternatives for administration. Crushing tablets or capsules to aid administration is tempting; however, concerns often arise regarding potential toxicity to the person who manipulates the medicine and efficacy changes due to manipulation of these medications [1].

There is low-level evidence for extemporaneous compounding of oral anticancer agents, as most data from primary literature consists of single case reports or studies assessing the stability of these agents in solutions and suspensions [2]. Additionally, manipulating tablets or capsules can alter the pharmacokinetics of the oral anticancer agent, possibly leading to decreased efficacy or safety.

This report delves into the specifics of everolimus, a first-generation mTOR inhibitor used in pediatric oncology and at the same time a medicine, that meets at least one NIOSH criterion for a hazardous drug [3].

Case presentation

A 7-year-old girl (weight 22kg, height 120cm) was diagnosed with diffuse intrinsic pontine glioma (DIPG) mTOR mutant, WHO grade IV in August 2024. DIPG is the most aggressive pediatric brain tumor with the median survival approximately 9-10 months [4,5] with limited treatment options since surgery is not feasible due to the location of the tumor and radiotherapy offers transient efficacy. Therefore, targeted therapies have been in the focus of research to offer possible advantages for patients with such dismal prognosis. Our patient was treated with targeted therapy with mTOR inhibiitor everolimus in combination with 54 Gy radiotherapy [4]. Oral everolimus at a dose of 5 mg orally once daily (5 mg/m^2) [4] was initiated in August 2024 and continued until progression in January 2025. Following recurrent episodes of severe stomatitis and myringitis which was considered a dose-dependent adverse effect of everolimus [6], the dose was reduced to 2.5 mg in December 2024 followed eventually only by some and not severe episodes of aphthous lesions in the mouth. However, since the 2.5 mg tablets or 5 mg tablets with a score line were not available on the market, extemporaneous compounding of this dose at the hospital pharmacy became necessary.

The automated compounding process involved using commercially available 10 mg everolimus tablets (Afinitor®, Novartis) which were crushed under the laminar bench and mixed in the disposable mixing jar with Polysorbate 80 (Caesar & Loretz GmbH) and a CuraBlend® gel

tablet excipient base (CurifyLabs Oy, Helsinki, Finland) using an automated mixer Gako PM140 (Gako Deutschland GmbH, Scheßlitz, Germany) for 10 minutes at 2800 RPM (Figure 1). The resulting formulation was transferred into a disposable syringe (CurifyLabs Oy, Helsinki, Finland) and printed with into 3/16" Mini Medi-Cap® Plus™ Blisters to create gel tablets of 545 mg, containing 2.5 mg of everolimus each.

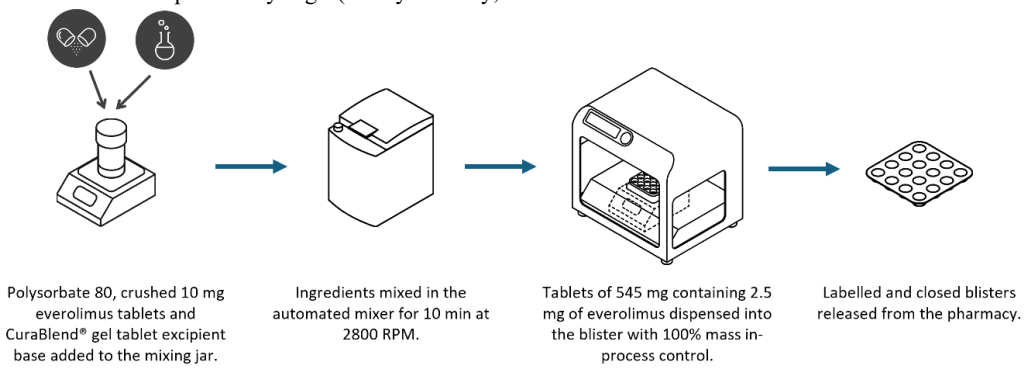

Figure 1: The automated compounding process using everolimus tablets, CuraBlend® gel and CurifyLabs Pharma Printer

Approximately one month after the start of using printed 2.5 mg everolimus tablets, the patient's everolimus plasma concentration was measured routinely and found out to be at 3.5 mcg/L, which falls within the reference range of 3-8 mcg/L. This shows the acceptable bioavailability of printed extemporaneous formulation. Unfortunately, in January 2025, the radiological progression of the disease was observed in MRT images requiring change in treatment schedule.

A manufacturing protocol was established for everolimus 2.5 mg doses which can be used in the future for patients requiring similar type of treatment.

Discussion

The literature identifies best practices for manipulating oral anticancer agents, noting that some should only be compounded in controlled environments [7]. Most current evidence mainly consists of individual case reports and stability studies of compounded formulations.

The risk of hazardous materials exposure for healthcare workers and caregivers is significant and must be thoroughly considered during compounding. Safety data available from studies on sterile compounding indicate that using an automated process of formulation preparation also for non-sterile products, such as automated mixing in the disposable container, and dosing the formulation into the final packaging with integrated mass uniformity control in place, reduces the risk of exposure to hazardous products in the compounding process [8].

Tailoring the dose to reduce the occurrence of dose dependent adverse effects was possible with a compounded product, while maintaining the target everolimus plasma concentration, which is a common practice in treatments with cytotoxic agents [9]. The compounding approach taken in this case aligns with safety guidelines and emphasizes the need for individualized dosing in pediatric oncological treatment [7,10,11].

Conclusion

This case underscores the importance of flexibility and innovation in managing pediatric oncological therapies. Through careful compounding practices that allow a contained manufacturing process, we successfully provided the required dosages of everolimus, ensuring continuity of care for our patient. The case shows that under-served patient populations such as children and cancer patients will benefit from automating the non-sterile drug compounding process in pharmacies and more tailored approach to personalization of medicines.

Ethical Approval Statement: Ethics approval has not been obtained for this case report as the treatment was run as standard of care. The extemporaneous compounding of everolimus was result of a non-existing age-appropriate paediatric formulation.
Parental approval was received for publishing this case report.

Competing Interest Statement:

Jana Lass, Kristjan Olado and Marika Saar have no conflicts of interest to disclose.

Niklas Sandler and Ludmila Hrizanovska work for CurifyLabs and have developed the technology used in the study.

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