RESEARCH LETTER

blood advances

TO THE EDITOR:

Tagraxofusp for blastic plasmacytoid dendritic cell neoplasm: a 2-speed cure in the United States and European Union

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Although it has been only a few years since a nosographic framework had been developed for blastic plasmacytoid dendritic cell neoplasm (BPDCN), a clear diagnostic work-up has already been established, facilitating a correct diagnosis.[1] Nevertheless, BPDCN continues to be misdiagnosed or confused with other neoplastic pathologies, often resulting in a dramatic delay in initiating appropriate treatment, leading to a decisive worsening of the prognosis of the patients.[2]

Until 5 years ago, BPDCN was considered an orphan disease, and although it has been acknowledged as a clonal proliferation of myeloid progenitors, no standardized therapeutic approach has been established; clinicians generally attempt numerous forms of treatment, including acute myeloid leukemia–like, acute lymphoblastic leukemia–like, and lymphoma-like approaches, often obtaining transient responses and poor overall survival.[1,3,4] Allogeneic hematopoietic stem cell transplantation remains the only potentially curative treatment for BPDCN. Even so, only a minority of patients are candidates for allogeneic hematopoietic stem cell transplantation, given the preponderance of disease among older individuals.[4]

In 2018, after years of research and development, BPDCN received its first targeted therapy, the CD123-based fusion protein SL-401 (tagraxofusp), consisting of interleukin-3 linked to the C-terminus of the truncated diphtheria toxin.[5] Tagraxofusp internalizes into target cells by binding surface interleukin-3 receptor-α (CD123) and inhibits cellular protein translocation by adenosine 5′-diphosphate ribosylation of eukaryotic elongation factor 2, subsequently causing cell death.[6] The pivotal study conducted by Pemmaraju et al was a phase 1/2 clinical trial showing a 90% overall response rate, and it led to the licensing of tagraxofusp for BPDCN by the Food and Drug Administration (FDA) on 21 December 2018.[7] Since then, the drug has been available in the United States as a treatment for all patients with BPDCN aged ≥2 years. In August 2019, the manufacturer launched an expanded access program (EAP) in Europe in order to guarantee patients' access to tagraxofusp before its approval by the European Medicines Agency (EMA) and, at the same time, collect data on its efficacy and safety in everyday clinical practice.[8] The European EAP was a single-arm, retrospective, multicenter observational study involving both patients with treatment-naive BPDCN and other-relapsed/refractory BPDCN treated with tagraxofusp in real life in 6 European countries (France, Germany, Italy, Switzerland, Austria, and Spain).[8] The preliminary analysis of the EAP revealed extremely satisfactory data and a favorable risk-benefit profile of tagraxofusp, with an efficacy that appeared even higher than that reported in the registration trial.[9] Despite the excellent results, it was several years after FDA approval, on 7 January 2021, that the EMA granted marketing authorization in the European Union (EU) for tagraxofusp as frontline therapy in BPDCN, limiting its use as a monotherapy treatment to adult patients (aged ≥18 years). Nonetheless, the drug is still under evaluation by the regulatory agencies of most European countries, whereas it has been available only in Germany since January 2023 and secondly in Italy, where the Italian Medicines Agency-AIFA has approved the reimbursement of tagraxofusp in March 2023. The Spanish Agency for Medicine and Health Products has declared in March 2022 that

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tagraxofusp is among the 5 oncological drugs authorized by the EU in 2021, which are not still registered in Spain, because the owner laboratory has not yet requested it.[10]

Actually, there are 2 major concerns in the EU: first, the fact that tagraxofusp is not yet accessible to adults with BPDCN in most countries of the European community and second, the drug is not available for pediatric populations throughout Europe. Of note, after a marketing authorization has been granted, decisions about price and reimbursement take place at the level of each EU member state, considering the potential favorable role and the use of the medicine in the context of the national health system of that country. This implies that, following the local regulatory process, the negotiation for placing a new drug on the market takes a long time.

Regulatory agencies face constant pressure to speed up the development, review, and approval of drugs for serious diseases. Both the FDA and EMA support clinical drug development and accelerated review and authorization procedures. These programs are intended to meet the expectations of drug manufacturers and patients, the former ready to launch new drugs promptly to maximize the return on investment and the latter to have access to potentially innovative therapies as soon as possible. Although the companies apply almost simultaneously to the FDA and EMA, most often new drugs are allowed into the European market only after they have been authorized in the United States. Differences, in fact, exist between the FDA and EMA in the way of reviewing and licensing drugs; the FDA's approach is more biology driven, whereas the EMA's methodology is more oriented to clinical evidence. This might refer to the connection between the EMA and the member states, which tends to base decisions on pricing and reimbursement on clinical rather than preclinical data. In Europe, such delays are more likely to be mainly because of the lengthy process of adoption of new medicines and, above all, the price negotiation at a national level. This means that large patient populations, such as the Europeans, cannot benefit from effective treatments for serious diseases, which have already been available in the United States for months.

Pharmacological research by industry is extremely expensive, and, inevitably, new drugs have significant costs. Tagraxofusp is administered IV in a 15-minute infusion, once daily for 5 consecutive days every 3 weeks, at the recommended dose of 12 μg/kg. The cycles are repeatable. Treatment is continued until disease progression or unacceptable toxicity.[6] The price of tagraxofusp concentrate for solution for intravenous infusion (1 mg/mL) is ~$32 561 for a supply of 1 mL, whereas in Europe it is €38 502.78 per mL. The high costs represent an economic barrier to accessing tagraxofusp, even in countries where it is authorized. In addition, in Europe, health care is public and paid directly by the state, whereas in the United Stated the health care system is mainly covered by private insurance. Unfortunately, patients with rare diseases such as BPDCN pay the highest cost, without any benefit from such as therapeutic innovations. This problem is not easy to solve, and it may be applied to other advanced treatments, such as chimeric antigen receptor T-cell therapy in the hematologic setting.

The scenarios in the rest of the world are even more challenging. In countries other than the United States and European ones, patients with BPDCN currently have limited treatment options. As recently as 1 September 2023, tagraxofusp has been designated by the Ministry of Health, Labour and Welfare of Japan as an orphan drug for BPDCN. The orphan drug designation is intended for therapeutic use in <50 000 patients with particularly high medical needs. This can potentially shorten the period required to obtain regulatory approval in Japan by several months, thereby enabling faster patient access to the drug. To date, there is no information on the availability of the drug in the rest of Asia or in developing countries.

Definitely, the approval of tagraxofusp for the treatment of BPDCN in December 2018 drastically changed the treatment landscape for patients with this rare neoplasm in the United States, where the clinical research has gone even further. As happens for other monoclonal antibodies, neoplastic cells can develop resistance to tagraxofusp; the main mechanism in BPDCN seems to be regulated by DNA methylation and downregulation of diphthamide genes rather than by CD123 loss.[11] Diphthamide silencing is reversible by the administration of the hypomethylating agent azacitidine, which restores tagraxofusp resistance in xenograft models.[11] Likewise, cells resistant to tagraxofusp show an increased apoptotic priming and dependence on the antiapoptotic protein BCL2, suggesting a high sensitivity to venetoclax.[12] Several clinical trials are ongoing in the United States to enhance the cure rates for BPDCN, investigating association with doublets and even triplets of drugs, combining tagraxofusp with different chemotherapeutic agents to overcome the occurrence of tagraxofusp resistance (eg, tagraxofusp/azacitidine/venetoclax and tagraxofusp/cyclophosphamide, vincristine sulfate, doxorubicin hydrochloride (Adriamycin), and dexamethasone; ClinicalTrials.gov identifier: NCT03113643 and NCT04216524, respectively). At the same time, different active clinical trials for the treatment of BPDCN with other new drugs, such as IMGN632 (pivekimab sunirine) include very few European sites for clinical trial entry.

What should we expect in the coming years? Realistically, in the EU the gold standard for BPDCN will remain the conventional chemotherapy approach, with clinical researchers continuing to try to design more effective protocols based on "old" drugs with obsolete scheduling for patients with this rare but unrelenting pathology.[13]

In conclusion, it appears evident that EMA and FDA approval processes on oncology drugs have important divergences. These differences in access to treatments in such a globalized world may have important consequences, significantly affecting, above all, access of patients with cancer to relevant therapeutics. Further efforts on harmonizing decision making between the main regulatory systems are required to get the best out of available data for the sake of patient benefit and public health worldwide.

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