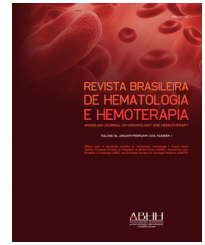




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### Editorial

# Paradoxes of hematology: When the old disappears and the new does not arrive



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Over the last few decades, we have seen considerable progress in cancer treatment with patients surviving for ever-increasing times. An important part of this progress is the result of new drugs with mechanisms of action distinct from classic chemotherapy, sometimes based on disease control rather than cure. However, despite the great advances, many drugs developed in the 60s, 70s and 80s are among the mainstays of the curative treatment of leukemias, lymphomas and solid tumors until today.<sup>1,2</sup> Even having extreme importance, these old, cheap drugs have disappeared from the market in the last decade, prejudicing the treatment of many patients because there is no substitute for them. For us physicians and for patients the question remains: why do cheap but essential old medicines disappear while modern and increasingly expensive medicines appear in the market daily? The answer

seems simple: the old drugs are cheap and the pharmaceutical industry no longer has any interest to produce them.

This, however, is only part of the answer. The reasons are diverse, but not always easy to understand, as pharmaceutical companies do not reveal their production policies or marketing strategies.<sup>3-5</sup> We know that the legal and sanitary requirements to produce medicines are always increasing. This is clear when we notice that injectable drugs have disappeared the most. With the new requirements, factories need to make adjustments during which production is interrupted. The lack of a patent often leads to production by a limited number of companies with this number being insufficient to supply the international market. The estimate is that at least four factories of a particular drug are needed to reduce the risk of a drug shortage to the minimal. With the difference in

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price between reference and generic medications, the interest in producing these medicines has fallen drastically. In rich countries, the 'renewal' of technology is part of the strategic process of the pharmaceutical industry that recompenses the nation with taxes, jobs and dividends to shareholders.<sup>3,4</sup> For us, people from low- and middle-income countries, the shortage of old and effective drugs is a serious threat to the health system and to the chances of cure for cancer patients, especially those depending on the public system.<sup>5-7</sup>

The lack of medications starts a snowball that further worsens the already critical situation. With the fear of a break in the supply, many hospitals will stock drugs leaving other hospitals without any stock whatsoever. The strongest wins, in this case the richest. The price is yet another issue. If they are cheap, due to the law of supply and demand, we pay a higher price for drugs that are missing from the market.

What does the law say? Current legislation is weak in respect to curbing both shortages and high prices. In Brazil, as well as abroad, it is only necessary that the pharmaceutical laboratories warn one year in advance that they will no longer market specific drugs and nothing else. This is the legal requirement. Is that enough time for local authorities to organize themselves? Is there any other way to stop interrupting the delivery of essential medications since the unavailability of these drugs can affect the treatment of thousands of patients by substantially limiting their chances of cure? Are the authorities sufficiently aware about how the shortage of these medicines affects patient care?

The current episode with the suspension of oral and intravenous melphalan and chlorambucil and the situation related to asparaginase are examples of situations that show us that the Brazilian health authorities are still unaware of the seriousness of the absence of these drugs.<sup>5,7</sup> It is essential that the delay before taking action is much shorter than we have seen until now.

There is also no plausible explanation for the shortage of thalidomide, which is manufactured by a state laboratory and used to treat myeloma, myelodysplasia and myelofibrosis in the area of hematology in addition to its role in leprosy.

On the other hand, we are now experiencing another drama with the advent of new drugs that break paradigms, increase survival, decrease toxicity, improve quality of life and transform lethal diseases into chronic ones.

Imatinib has revolutionized the treatment of chronic myeloid leukemia (CML); we already have many patients treated for almost 17 years who do not show signs of disease.<sup>8</sup> Even in our scenario, we were not only able to treat these patients, but also produce numerous scientific articles and participate in various protocols and studies.<sup>9</sup> After Imatinib we have already reached second and third generation tyrosine kinase inhibitors. The example of CML is one of the best and most interesting. With the breaking of patents over time and negotiations between the Ministry of Health and laboratories with the forceful participation of hematologists, patients have access to medicines and their progress can be monitored with molecular biology tests following protocols recommended by several international groups.<sup>10</sup>

Another drug that changed the treatment and survival of patients with lymphoid diseases is rituximab. Thousands of patients of all ages with B lymphomas had their disease

cured, or their survival significantly increased with this drug developed about 20 years ago. Patients with chronic lymphocytic leukemia (CLL), a disease still considered incurable, have gained years of survival with this new medication. More recently, obinutuzumab and ibrutinib have been added to the drug arsenal, but unlike the history of CML, CLL, even though it is a leukemia and chronic disease, is an example of inconsistency both in our regulatory system and in our public health system. While treatment continues to advance, in the Brazilian public health service, named the *Sistema Único de Saúde* (SUS), patients are tied to treatments used for almost 60 years, such as chlorambucil and at most they receive fludarabine and cyclophosphamide, but without an important drug, rituximab. This is just one example demonstrating that, depending on the social class and the access to a good healthcare plan, patients may or may not enjoy a greater chance of an adequate response to treatment. A contradiction, in a country that has defined that all citizens have the right to health in its constitution. Looking at regulatory and market aspects, we were struggling to include an old but efficient drug, bendamustine, in the Brazilian market; this finally seems to have happened in 2017. This is a cheap drug used in the treatment of CLL that could improve the lives of thousands of SUS patients and those insured by health care providers.

Another paradox exists in the case of multiple myeloma. Bortezomib, used as first line treatment throughout the world, is not accessible through the SUS. The greatest irony lies in the fact that in Decree number 708 of August 6, 2015 issued by the Brazilian Health Ministry itself, bortezomib appears as the first-line drug to treat patients with multiple myeloma, but without reimbursement for its use.<sup>11</sup> Carfilzomib is already approved and daratumomab, a monoclonal antibody, should be approved soon. None of these will be made available to the SUS and, given the high cost of these medications; even health insurance plans will have difficulties to pay for the treatment. Lenalidomide has been on the shelf of the Brazilian regulatory board, the *Agência Nacional de Vigilância Sanitária* (ANVISA), for eight years and in developed countries, more potent drugs, such as pomalidomide, are already a reality.

As doctors we live a very serious situation, with irreplaceable drugs disappearing from the market and a range of new efficient but expensive drugs appearing. We have no hope that the Brazilian public health system will provide the new drugs to SUS patients in the short or medium term. It is the worst of the worlds, treatment has become very expensive because of the new drugs, but patients will suffer the consequences in terms of survival because the old drugs are missing. Even in the most modern protocols, there is no recommendation to substitute effective drugs, such as melphalan and L-asparaginase for other newer compounds.

Here we make a proposal: It is time for everyone involved in this issue to set up a positive agenda and plan access to these treatments. Costly drugs and complex procedures should only be used in public or private referral centers. Price adequacy and rational use of this arsenal should be addressed through meetings between all the players involved such as representatives of the pharmaceutical industry, medical societies, patient associations, health plans, the ministry of health, with the involvement of the three powers and the federal, state, and municipal governments.

We can no longer avoid or postpone the discussion on this serious problem! We have to guarantee access of Brazilian citizens to minimally adequate treatments in a fair and transparent process within possible cost restraints.

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### Conflict of interest

The authors declare no conflicts of interest.

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