Editorial

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

Angelo Maiolino\textsuperscript{a,b}, Belinda Pinto Simões\textsuperscript{c,d,\ast}, Claudio Galuão de Castro Junior\textsuperscript{e,f}, Dimas Tadeu Covas\textsuperscript{g}, Gustavo dos Santos Fernandes\textsuperscript{h}, Nelson Hamerschlag\textsuperscript{i,j,k}, Teresa Cristina Cardoso Fonseca\textsuperscript{e}, Vergilio Colturato\textsuperscript{c}

\textsuperscript{a} Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular (ABHH), Comitê de Mieloma Múltiplo, Brazil
\textsuperscript{b} International Myeloma Foundation-Latin America (IMF), Brazil
\textsuperscript{c} Sociedade Brasileira de Transplante de Medula Óssea (SBTMO), Brazil
\textsuperscript{d} Latin American Bone Marrow Transplant Association (LABMT), Brazil
\textsuperscript{e} Sociedade Brasileira de Oncologia Pediátrica (SOBOPE), Brazil
\textsuperscript{f} Santa Casa de Porto Alegre, Unidade de Hematologia/Oncologia Pediátrica, Porto Alegre, RS, Brazil
\textsuperscript{g} Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular (ABHH), Brazil
\textsuperscript{h} Sociedade Brasileira de Oncologia Clínica (SBOC), Brazil
\textsuperscript{i} Universidade de São Paulo (USP), Faculdade de Medicina, São Paulo, SP, Brazil
\textsuperscript{j} Hospital Israelita Albert Einstein, Programa de Hematologia e Transplante de Medula Óssea, São Paulo, SP, Brazil
\textsuperscript{k} Associação Brasileira de Linfoma e Leucemia (ABRALE), Brazil

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.\textsuperscript{1,2} 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.\textsuperscript{3-5} 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

\textsuperscript{\ast} Corresponding author at: Universidade de São Paulo, Faculdade de Medicina de Ribeirão Preto (FMRP-USP), Av Bandeirantes 3900, Monte Alegre, 14048-900 Ribeirão Preto, SP, Brazil.
E-mail address: bpsimoes@gmail.com (B.P. Simões).
price between reference and generic medications, the inter-
est in producing these medicines has fallen drastically. In rich
countries, the ‘renewal’ of technology is part of the strate-
gic process of the pharmaceutical industry that recompenses
the nation with taxes, jobs and dividends to shareholders.3,4
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.5–7

The lack of medications starts a snowball that further wors-
ers the already critical situation. With the fear of a break in
the supply, many hospitals will stock drugs leaving other hos-
pitals 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 pharmaceu-
tical 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 orga-
nize themselves? Is there any other way to stop interrupting
the delivery of essential medications since the unavailabil-
ity 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 intra-
venous 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 seri-
ousness of the absence of these drugs.5,7 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 trans-
form 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.8
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.9 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.10

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 lym-
phocytic 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 inconsis-
tency both in our regulatory system and in our public health
system. While treatment continues to advance, in the Brazil-
ian 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, ritux-
imab. 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 con-
stitution. 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.11 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 regula-
ory 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 expen-
sive 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 rec-
ommendation 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 represen-
tatives 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.

**Conflict of interest**

The authors declare no conflicts of interest.

**REFERENCES**