Following doctor's orders doesn't usually mean making a two-hour round trip to visit your hospital twice a week to beg for any spare medication on the off-chance that someone has had to change to a different drug, or was able to stop taking it, or had died.

But that's what it meant for Anna Maria Delgado, whose survival depends on access to a drug that she will need to take every day for the rest of her life.

Delgado (not her real name) was diagnosed with chronic myeloid leukaemia CML in 2021, after presenting at an accident and emergency department in Mexico City, acutely ill, and with a spleen that was twice the size it should have been. She was started on imatinib, which the haematology department provided for free, from a small stockpile it had built up from donations given by patients who had stopped taking their own prescriptions for one reason or another.

She responded very well to the drug, and little more than three months down the line, her spleen had shrunk back to a healthy size. Delgado was told that, to stay out of danger, she would need to take the prescribed dose of imatinib on a regular basis, and remain on the drug probably for the rest of her life. She was also told that, unfortunately, as the hospital could no longer provide it for her, she would need to find a way of accessing the drug herself.

Delgado can't do that, at least not in the longer term. She is no longer fit enough to earn her living as she used to, working in domestic service, cleaning and cooking. Together with her two grandchildren, she now relies solely on the meagre income that her daughter can earn from "selling things" and the occasional domestic job. The absolutely lowest possible cost of her imatinib prescription (a generic accessed through voluntary support associations) is around US$280 a month – a sum that is roughly equivalent to a month's rent. Little wonder then that Delgado resorted to hanging around the hospital dispensary begging for whatever could be spared – which as it turns out was not a lot.

"Since I found out that they gave them on Tuesdays and Fridays, I went every Tuesday and every Friday to see if someone could give me a little bit. I would talk to the people who were taking it to see if they could sell me, even if it was just a little tablet or something like that. And yes, two people sold me a little tablet.

"[My doctor] told me to keep insisting, to see if any of the patients stopped coming or were no longer interested in the medication, and that I should be on the lookout to see if I could fill that place. For a month I went twice a week to see if I could achieve something, but I did not, to tell the truth."

## The ground-breaking Glivec access programme

Stories like Delgado's are setting off alarm bells within the CML advocacy community. This highly active internationally networked group of advocates grew up over the past 20 years in direct response to the development of imatinib – one of the first, and still the most effective, precision drug in oncology – which offered the prospects of a normal life for people with this particular form of blood cancer.

With a presence in more than 90 countries, and networked within global organisations such as The Max Foundation and the CML Advocates Network, these advocates were part of a remarkable international humanitarian effort to ensure that access to this revolutionary small molecule could be provided to everyone who could benefit. That effort included schemes, led by the International CML Foundation, to train up haematologists around the world in how to correctly diagnose and manage patients. Perhaps the most crucial element, however, was the Glivec International Patients Assistance Program (GIPAP), which was established by Novartis – the company that developed

imatinib (brand name Glivec).

Set up in 2002, only a year after Glivec had been approved by the US and European regulators, GIPAP was ground-breaking not just in its ambition to ensure poverty should be no barrier to accessing Glivec anywhere in the world, but also in the way it was administered. Novartis set up a direct-to-patient assistance programme, and gave responsibility for running it to The Max Foundation, a small global CML patient advocacy group that had been launched five years earlier, in Seattle, Washington, by Pat Garcia-Gonzalez among others, in memory of her step-son Max.

The programme became a catalyst that spawned a global proliferation of CML advocacy groups, which worked with The Max Foundation to educate patients about their disease and offer support and advice, including on ways to access treatment.

The GIPAP programme also developed a global network of around 600 haematologists, as Glivec was supplied only to patients treated by doctors who were registered with The Max Foundation as having had the necessary training in diagnosing and managing the disease.

> GIPAP ran in 80 low- and middle-income countries and provided more than 100 million doses of Glivec around the world

During its 13 years in operation, GIPAP ran in 80 low- and middle-income countries and provided more than 100 million doses of Glivec around the world, saving and transforming the lives of close to 100,000 patients. But in the course of those 13 years, as Novartis launched commercial operations for Glivec in some of those countries, GIPAP was closed to new patients. That was the case in Mexico, where Novartis closed the GIPAP programme in 2015, which is why that lifeline was not available to Anna Delgado when she was diagnosed with CML in 2021.

## A troubled transition to commercial access

In many middle-income countries where GIPAP was originally established, like Vietnam or Thailand for instance, CML and GIST patients can now expect, with reasonable confidence, to access the treatments they need, on a regular basis, through their own health services.

But things are more complicated in other countries, as Max Foundation's Garcia-Gonzalez explains. First there is a group of countries at the lowest end of the income scale where there is currently no prospect for governments to provide access even to generics. For these countries, Novartis has agreed to continue to provide the drug to patients who cannot afford it and have no other means of access, she says.

This they do via an access programme that The Max Foundation launched in 2017, which is also supported by the four other pharmaceutical companies that have entered the CML/GIST space over the past decade – Bristol-Myers Squibb (Sprycel/dasatinib), Takeda and Incyte (Iclusig/ponatinib) and Pfizer (Bosulif/bosutinib). "Most companies are OK with low-income countries. We have around 35 countries around the world today where we can give a patient any of these TKIs [tyrosine kinase inhibitors]," says Garcia-Gonzalez. It's when you get to low-middle income or middle-income countries, she says, "where things get more challenging".

Among countries that struck a commercial procurement deal with Novartis, patients who had been on the GIPAP programme switched to get their Glivec via the state, explains Garcia-Gonzalez. But

others struck deals with generics providers, in which case Novartis often agreed to continue to provide Glivec, but only to patients who were already in the programme. “There’s about 13 countries or so where we continue to help the patients that were originally in the GIPAP programme, but we have agreed with the company that we will not take new patients.”

> “The Max Foundation receives desperate emails every day, from patients in several countries, including Mexico”

The problems for patients like Delgado, explains Garcia-Gonzalez, tend to arise in countries where supposedly there is access to generics, “but either the generics are not good, or the government purchases sometimes, but there is not really continuous access to those drugs.” These countries are typically in the ‘grey area’, says Garcia-Gonzalez – not low income, not high income. “One would wish governments would provide these treatments, but they are falling through the cracks.”

As a consequence, says Garcia-Gonzalez, The Max Foundation receives “desperate emails every day, from patients in several countries, including Mexico, where things did not work in the way they were supposed to work as we were transitioning to government programmes… We have felt a lot of pressure and concern for patients. When the government is not able or willing to provide the drug in the way they should, it is tragic. Even with generics in the markets in these countries, no one can afford these generics.”

She believes that what is happening now in CML could have wider implications for efforts to improve access to cancer care at a global level. “The assumption that when a company loses exclusivity this drug will be widely available through generics for a disease like CML – it’s not what happens,” she says. And if it’s not happening for imatinib – a TKI – what chance that access will be any better for the many biological therapies that account for so much of the precision medicine armoury in today’s oncology, which are more difficult and costly to manufacture, and less effective?

## Universal access to cancer care – theory and practice

Global efforts to encourage and assist low- and middle-income countries to build capacity to meet the needs of escalating numbers of cancer patients have tended to focus on two related policy areas. The first has been to hitch their wagon to the cause of ‘universal health coverage’ – a policy widely pursued by the global health community whereby access to healthcare is guaranteed to all citizens, not just those who can afford it. The second has been to argue the case for essential cancer diagnostics and treatments to be included in the package of care covered by universal coverage systems – which has involved challenging widely held assumptions about cancer being largely a ‘Western’ health problem and about the cost–benefit of investing in early/accurate diagnosis and effective care.

Mexico, as it happens (population 128 million), was an early poster child for this approach. The country took its first steps towards universal healthcare provision in 2002 when it set up Seguro Popular – a health insurance system for its poorest citizens who were not covered by any other insurance schemes, such as those available to people employed by commercial companies or working in the public sector. Enrolment was practically free, and gave access to free basic healthcare.

Cancer diagnoses began to be covered in 2007, starting with breast and cervical cancer, and

extending later to non-Hodgkin's lymphoma, testicular and prostate cancer, and bone marrow transplants. For children under 18, all neoplasms were covered. Then in 2020 came a major change of approach, with a focus on delivering healthcare services through public provision, under the auspices of INSABI – a new Institute of Health for Wellbeing – and a new system for procuring drugs.

Under the new system, coverage is no longer limited to a defined list of conditions, and it seems imatinib is now available on the public health system, at least in theory. In practice, however, a large number of patients covered by INSABI, like Anna Delgado, remain unable to get access. Indeed, some of the treatments guaranteed under the previous system are currently unavailable – or have intermittent or restricted availability.

> Guzman believes the problems are largely bureaucratic, arising from the major changes to procurement and service delivery

Delgado's doctor, Tomás Guzman (not his real name), believes the new system could be made to work. He has no issues with the efficacy or safety of the generic now being used in the public health system. "The experience I have is that it has been good, it has had good tolerance, a side effect profile similar to that of the patent drug," he says, adding the caveat that more time will be needed for greater certainty.

Consistent, reliable access does, however, seem to be an unresolved problem, at least for those who are unable to pay and are not eligible to enrol in the social security systems run for public and private employees. Guzman believes the problems are largely bureaucratic, arising from the major changes to procurement and service delivery – and the timing of these changes, just as the Covid pandemic hit, won't have helped. "There was a period of time in which it was not even possible to buy it, and there was not enough medicine to supply all the patients."

He sees hopeful signs that things may be getting more organised. "I am beginning to see that this is changing, fortunately, and now there are already patients with recent diagnoses, at least in some hospitals, who are already able to receive free treatment." But as he points out, many patients are still falling through the gaps. "It is not homogeneous across all INSABI hospitals. I talk to many colleagues, and there are some where it still does not arrive. I do not know why. The truth is that I cannot see what the obstacles are for this not to be happening."

"Fortunately, there are many people who are involved with this disease," he adds. "There are many associations, there are also many patients who sometimes have medication to spare."

The Mexican Leukaemia and GIST Association (AMELEG) is one of the associations mentioned by Guzman that supports and advocates for patients and is able to negotiate discounted access to imatinib for its members.

AMELEG President, Martín Rosales de la Rosa, says they have around 500 members, and receive around 20 to 25 new applications every month. Many of the applicants are theoretically covered by INSABI, and should have free access to the medication via the health service, but in practice that is clearly not happening.

AMELEG is able to help most new applicants, he says, but there are always a few for whom no solutions can be found. Some end up halving their dose, even though they know it is very dangerous.

Some can't even afford the half dose "There are patients who have let themselves die," says de la Rosa.

## A wider problem

As Garcia-Gonzalez from The Max Foundation points out, it's not just in Mexico where patients are falling through the gap between what is promised and what is delivered by universal healthcare systems. Similar scenarios seem to be playing out in other middle-income countries such as the Philippines (population 110 million), where a law was passed in 2019 that extended universal healthcare – PhilHealth – to cover costs of care for all types of cancer. This meant, at least in theory, that treatments for chronic myeloid leukaemia would be covered for the first time.

Previously the only cancers covered by PhilHealth had been breast, prostate, cervical and paediatric acute lymphocytic leukaemia (since 2011) and colorectal (since 2015).

In the Philippines, Glivec did not come off patent until 2020. The government then put the contract for imatinib out to tender and awarded the contract to Novartis at a cost that is unknown, but presumably not far from the price quoted by generic manufacturers also tendering for the contract. That medicine was then made available under PhilCare through the Blood Cancers Access Program, which was started in December 2020.

But, as happened in Mexico, access via PhilHealth has been severely restricted, with only around 100 patients having access according to data from August 2021 – a small fraction of expected need in a country with a population of 100 million. Roderick Mugas, a 44-year-old pedal rickshaw driver from Caloocan, a few kilometres from the capital city Manila, was one of the lucky ones. After the changes came in, Mugas was able to go to the Department of Health central office at the Philippine General Hospital in Manila to pick up a month's supply of imatinib, for free.

"I have no idea where I would get the 13,353 pesos (US$250) which is the cost of the medicines I need every month if I were not with the [Blood Cancers Access] Program," he told *Cancerworld*. "There is just no way we can afford it. If I lose access, I have no option but to leave my fate and that of my family to God."

Mugas, who earns around US$7 a day pedalling passengers and goods around the city, was diagnosed with CML in 2018. Too late to benefit from the GIPAP access programme, which closed to new patients in 2008, he initially relied on a local Novartis Philippines access programme, which used far more stringent criteria than GIPAP for giving free access. Even though his US$7 a day had to support a wife and two children, he still had to contribute towards the cost of his medicine.

Doing that meant that, every time his medication needed replenishing, he had to take several bus rides to and from various government agencies and spend hours queuing to ask for financial assistance from the Philippine Charity Sweepstakes Office, and then wait several days for the paperwork to come through.

According to Rod Padua, President of the Touched by Max CML patient advocacy group in the Philippines, it's a gruelling experience. "If you could see the queues in Philippines… If you are not sick before going there, you will be afterwards. Standing for hours shoulder to shoulder often in extreme heat – it's too much for the patients sometimes."

In June of this year the supplies dried up. "There are no available

> CML drugs under the programme, probably due to delays in procurement”

For Mugas, having free access to medicine not only freed him up from time spent queuing, it also allowed him to stay fit enough to continue the pedal rickshaw work that his family relies on. But when he spoke to *Cancerworld*, earlier this year, he was clearly worried about how reliable that access was. When *Cancerworld* made enquiries a few months ago, the reply came back “The Department of Health assures our cancer patients that the Cancer and Supportive-Palliative Medicines Access Program (CSPMAP) will continue and its fund for 2022 is very intact.” Yet in June of this year the supplies dried up. “There are no available CML drugs under the programme, probably due to delays in government procurement,” Padua reports.

Worse still, he says that even the option of queuing for hours for help to fund supplies for a month or two is now no longer open, due to the rocketing demand for assistance caused by the Covid pandemic. “My latest feedback from the [CML] patients is that they cannot now get a single cent from the charity sweepstakes. Maybe token money from the office of politicians [more queuing]. They give you 3000 or 5000 pesos [US$55–95] if you are lucky.”

## Collateral damage

That people are dying across the world for lack of access to effective cancer treatments is hardly news, and in terms of numbers, the toll inflicted by CML – a rare form of a rare cancer – pales into insignificance compared with the big cancer killers such as stomach, lung, breast, cervix and liver.

Yet the CML story is troubling for a number of reasons. TKIs are relatively easy to make, transport and store, and once a quality production facility is up and running, the incremental cost of increasing production is very low. Treatment requires no high-end facilities, no surgery, no radiotherapy. It does require diagnostic PCR testing, but new technologies, such as the cartridges developed by Cepheid, are making this much more accessible in terms of cost, logistics and expertise.

In short, when it comes to tackling cancer at a global level, this is the low-hanging fruit.

In addition, you have the human infrastructure that developed over the past 20 years. The doctors who were trained – many thanks to the efforts of the International CML Foundation – the CML patient advocacy groups that have a global reach unparalleled in any other cancer type, who are able to advise patients and channel them towards any treatment options open to them. And then The Max Foundation, which is now running what amounts to a supranational access service for some of the poorest CML patients, working with all companies producing CML TKIs, according to agreed eligibility criteria and across an agreed range of countries (which are not the same for all companies).

In other words, the administration and distribution systems are up and running, and ready to expand coverage to provide access to patients like Delgado and Mugas as soon as they get the nod.

As things stand however, it seems that nod is unlikely to be forthcoming for patients in countries like Mexico and Philippines, for reasons that are perfectly understandable. Responsibility for healthcare lies with governments, and if affordable drugs are available, and if commercial agreements are in place to procure imatinib, then companies argue that it is up to governments to ensure that all their citizens have access. Governments won’t take up that responsibility if they know companies will

provide the drugs for free.

> “You need to have systemic change where the governments step up to their own responsibilities. But what happens when they won’t?”

“I can see where they are coming from,” says Jan Geissler, who is a co-founder and on the steering committee of the CML Advocates Network. “If you take it from a purely methodological point of view, companies can’t give drugs for free in the long run. You need to have systemic change where the governments step up to their own responsibilities to serve their populations with drugs that save their lives.” But what happens when they don’t and won’t? he asks.

The answer, as he knows, is that many patients are end up as collateral damage, “People dying in the countries are more or less taken as the toll that should put pressure on the government to start providing the drugs.” What advocacy groups find hard to understand, says Garcia-Gonzalez, is that the companies could decide to help if they wanted to, “It’s not a big financial burden, it’s a principle problem.”

That’s not to say that the advocates don’t recognise the unparalleled generosity that Novartis in particular has shown with its original access programme, and continues to show in its commitment to provide access to patients through CancerPath to Care, its current collaboration with The Max Foundation. They do. But that doesn’t solve the problem of the many patients who are suffering and dying for lack of access right now – many of whom are in contact with advocacy groups pleading for help.

### ‘We were pioneers’

The issue has generated heated discussions between advocates and companies in recent years. Geissler says the companies have been reluctant to acknowledge the extent to which the stated policies of governments like those in Mexico and Philippines fail to be reflected on the ground.

They also argue, says Geissler, that it is the job of advocacy groups to lobby governments for better access, and that it’s a health system problem not just a CML problem, so they need to form alliances with advocates for other cancers.

> “The problem with our discussions is that it is always finger pointing”

Geissler counters that they always have, and still do, lobby for access, and have had some success in some countries, but many countries “just don’t care no matter how hard we try”. While alliances are a great idea, he adds, and are working well in higher-income settings, that can be hard to replicate in low/middle-income settings, where most global umbrella patient organisations don’t have anything like the presence of the CML advocacy community.

“The problem with our discussions is that it is always finger pointing,” says Geissler. In meetings

with the industry, he says, he advocates for a more collective response: “Everyone needs to do the maximum within their sphere of influence and responsibilities.” And he challenges the idea that nothing can move for CML patients until the whole health system moves for everybody.

Pointing to the ground-breaking access programme Novartis set up back in 2002, the number of patients it reached, how it transformed the training and advocacy landscape, he says, “We as CML have been the pioneers. Change it for CML and develop a model for other cancers side by side. In CML, we have the privilege of survival, which is why we have experienced advocates everywhere, we have the privilege of The Max Foundation being on the ground everywhere, we have the privilege of already having generics of a drug that has been a game changer in the treatment of a cancer, and many doctors who know how to diagnose and manage the disease. So we have all the puzzle pieces in place. All it needs is commitment that everybody does the maximum they can within their sphere of influence.”

For Geissler, the main point is that there is a conversation that needs to be had and that companies need to part of that.

*Cancerworld* invited Novartis and Bristol-Myers Squibb, the two companies with off-patent CML therapies, to comment.

Novartis said, “We agree with the community that access to medicines for CML and other cancers remains a challenge in many countries and share the concern of the CML patient community for patients who lack access.” They point to their record of having “provided free medicine to thousands of patients diagnosed with Philadelphia chromosome positive chronic myelogenous leukemia (CML) and other rare cancers in low- and middle-income countries (LMICs),” and to their current commitment to the Cancer Path to Care – “an innovative, access initiative which connects people living with CML, as well as breast and other cancers, with effective treatments, professional medical capabilities, trained physicians, and hands-on support,” through which they aim “to provide access to care to 36,000 patients in over 70 LMICs by 2025”.

And they point out that Novartis is the first pharmaceutical company to contribute an innovative treatment (nilotinib, their second CML drug, still on patent) to the Access to Oncology Medicines (ATOM) Coalition, launched in May 2022, to increase access to quality-assured essential cancer medicines in low- and middle-income countries. “We will grant Medicines Patent Pool [a UN-backed public health organisation] a freedom to operate license, which will be used to sub-license and work with identified generic manufacturers who will independently manufacture, register, and commercialize the generic versions in the local markets. The expectation is that this contribution will provide a new model, and a first step, for the sector to help close the gaps in access to life-changing medicines.”

The company says it will continue to play its part to provide access for CML patients, “and is committed to partnering with all stakeholders to create sustainable solutions that provide broad access to medicine for patients living with cancer.”

The Max Foundation’s Garcia-Gonzalez knows better than most Novartis’s history of valuable support for CML patients in developing countries while Glivec was on patent, as well as their continuing efforts. But she also knows that vast swathes of patients are continuing to fall through the gaps, particularly in countries where there is a formal government commitment to provide the drug that is simply not translating into reality.

“We have learned through Covid that it’s one thing to make drugs and vaccines available and it’s another for people to access them. It is very tough for patients of low socio-economic means to stay

on treatment for 20 to 30 years. To continue to go back to the doctor every two to three months. It is very hard for patients themselves. On the other hand, you have to make sure that when the patient shows up every three months there is enough drug to give them… That is also hard."

"So even in the best scenario that a government really is committed to these patients, logistics are difficult. And a disease like CML is a small disease in the middle of a million other diseases that governments would prioritise. This is where we see these things happening which is so tragic."

Geissler points to all the preparatory work done in high-income countries before introducing a new drug – including requests for companies to run post-marketing studies – and says it is maybe naïve to think that affordability is the only barrier preventing low/middle-income countries from adopting generics as they come onto the market. What is lacking is a national infrastructure, or a registry, which can gather data on the size and location of the patient population, and of the centres with expertise in diagnosing and managing CML, and log treatments and outcomes. Lack of local infrastructure and reliable local data is then used as an excuse not to provide access, he says.

> "When expensive cancer drugs lose patent, we cannot assume that generics will come and the problem is solved. The problem is not solved"

Much of that data gathering and networking was, of course, already done by The Max Foundation, using their own system. To help resolve what he calls "the conundrum of the transition", that needs to happen within the public health systems, argues Geissler. This is one area where he feels companies could help. The data, he says, would provide effective ammunition to doctors, patients and advocates lobbying their governments for reliable and equitable access. The infrastructure would mitigate many of the challenges faced by health departments and health services in predicting levels of demand and organising delivery across the system.

The message for global health and cancer strategists, says Garcia-Gonzales, is: "When these expensive cancer drugs lose patent, we cannot assume that they will come to many countries in the world… that generics will come, and the problem is solved. The problem is not solved."

"We need companies to do what they are doing, which is to continue to support even beyond the exclusivity, and that is something that, before imatinib, nobody imagined. That is one of the big lessons. Responsibility does not end with the loss of exclusivity.

"If patients are saying, 'I go to the doctor and the doctor tells me there is nothing that can be done for me,' Who is responsible? Where does responsibility start and end? I think that is the key to the tragedy for me. The company says, 'well we've done our part, we've helped patients until this point, now the government has passed this law. If we continue to provide, then the government will never provide.' So we need to create the environment to create the need for the government to do what they need to do. In the meantime, patients die for no good reason."

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