Access to Therapy for Acute Myeloid Leukemia in the Developing World: Barriers and Solutions

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Abstract

Purpose of Review Acute myeloid leukemia (AML) is a costly disease, and its impact is greater in developing countries (DC). We will review the current concept of what are DC, compare the differences in the epidemiology and economic burden of this disease between developed and DC, and finally, analyze the barriers and possible solutions that DC should implement to achieve better results.

Recent Findings DC is a frequently misunderstood name. The way we use to measure human development is changing, and multidimension metrics better define what are DC. With this in mind, we show the differences in the AML epidemiology and the impact of economic burden in DC. We analyze the barriers to access therapy from a clinician point of view, to show that most DC shared similar challenges but with a diverse healthcare structure. Finally, we provide several possible solutions for a more integrated and timely treatment that allows better results not only in terms of survival but with a better quality of life.

Summary The economic burden of AML treatment in DC is high, and the results are poor. It is crucial to face this challenge and propose new treatment approaches to achieve better results.

Keywords Leukemia · Acute leukemia · Acute myeloid leukemia (AML) · Developing countries · AML treatment · Healthcare

Introduction to AML

Acute myeloid leukemia (AML) has the highest incidence of adult acute leukemias in developed countries, with an estimated incidence of 4.3 new cases per 100,000 in the United States (US) in 2018 [1].

Acute myeloid leukemia (AML) is a hematologic malignancy characterized by clonal, abnormally differentiated cells of the hematopoietic system accumulating in the bone marrow, blood, and possibly other organs [2•]. Without treatment, survival is measured in days to weeks [2•]. Fit people with AML are usually offered induction chemotherapy, which

results in the achievement of complete remission (CR) in most cases. Still, despite post-remission chemotherapy and/or allogeneic hematopoietic cell transplantation (HCT), relapses are common and only a minority of the affected individuals will be long-term survivors [2•].

The 5-year overall survival (OS) rate for all AML patients in the US has improved modestly over several decades from 6.4% in 1975–1977 to 28.1% for patients diagnosed in 2008–14 [3]. Even in the selected patient population receiving intensive therapy, 5-year OS rate ranges between 25 and 40% and declines for older and intensive therapy ineligible patients where the long-term OS rate is less than 10% [4, 5].

After decades of minimal therapeutic progress, the pace of approvals has steeply accelerated with eight novel agents being approved in the US by the Food and Drug Administration (FDA) for subsets of patients with AML [6].

Given the heterogenous treatment approaches, the cost of AML has been difficult to estimate. Previous studies have shown that costs of AML treatment depend not only on treatment modality either intensive chemotherapy (HIC), HSCT, low-intensity treatment (LIT), or supportive care (SC), but

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also on insurance status and country of residence [7] and are largely driven by healthcare resources utilization [2, 4].

Further, complexity is increased because health care resource varies between different countries. Developing countries (DC) faced many difficulties to treat cancer, and the high economic burden of AML is a big challenge for them. Nevertheless, DC is an ambiguous term, and first, we need to clarify it and then analyze the barriers and possible solutions to obtain better results in the treatment of AML in these countries.

AML Data in DC

Defining Developing Countries: What We Should Know

Several studies performed in either DC, such as Brazil, or those with high ethnic and demographic diversities, such as the United States or the UK, demonstrated the association of the socioeconomic status (SES) with the access to HSCT and mortality after transplantation [8]. The distribution of some modalities of treatment in AML, like HSCT, varies strongly among countries, which, in major part, depends on economic conditions defined by the Gross National Income per capita [8]. On the other hand, it may be speculated that the background determining availability of diverse therapies may be more complex and may include socioeconomic factors other than gross national income [8]. In 1990, the Human Development Index (HDI) was launched with this underlying principle: National development should be measured not only by income per capita, as had long been the practice, but also by health and education achievements. HDI was commissioned by the United Nations Organization to evaluate a country's socioeconomic achievements in 3 basic aspects of human development: longevity, knowledge, and standard of living [9•]. Thus, HDI is a composite index focusing on three basic dimensions of human development: the ability to lead a long and healthy life, measured by life expectancy at birth; the ability to acquire knowledge, measured by mean years of schooling and expected years of schooling; and the ability to achieve a decent standard of living, measured by gross national income per capita. Nevertheless, assessing inequalities in human development (HD) demands a revolution in metrics. Over the years, additional indices have been developed to capture other dimensions of human development to identify groups falling behind in human progress and to monitor the distribution of human development [9•]. Recently, to measure HD more comprehensively, the Human Development Report presents four other composite indices: (1) The Inequality-adjusted HDI (IHDI) discounts the HDI according to the extent of inequality, in other words, with perfect equality the HDI and the IHDI are equal. Nevertheless, when there is

inequality in the distribution of health, education, and income, the HDI in a society is less than the aggregate HDI. The greater the inequality, the lower the IHDI (and the greater the difference between it and the HDI). The average loss in the global HDI value due to inequality is about 20% [10], but it is higher in countries with low HD; in these countries, the average HDI is 30% lower, but could be as wide as 45% lower in some regions of the world like Comoros in Africa [9•]. For health, vast inequalities exist across countries with different levels of HD. (2) The Gender Development Index compares female and male HDI values, worldwide; the average HDI value for women is 5.9% lower than for men, and the gender gap is widest in low HD countries, where the average HDI is 13.8% lower for women than for men. (3) The Gender Inequality Index was proposed in 2014 and highlights women's empowerment. (4) The Multidimensional Poverty Index (MPI) measures non-income dimensions of poverty. For instance, in low HD countries 47.5% of adults are illiterate and only 17% of the population has access to internet. The latest edition of HDI [9•] proposed four human development groups according these composite indexes: very high (HDI 0.894), high (HDI 0.757), medium (HDI 0.645), and low HDI (HDI 0.504). DC as a whole were placed between medium and high HDI with 0.681 and were divided by regions: Europe and Central Asia (HDI 0.771), Latin America and Caribbean (HDI 0.758), East Asia and the Pacific (HDI 0.733), Arab states (HDI 0.699), South Asia (HDI 0.638), and Sub-Saharan Africa (HDI 0.537) (Table 1) [9•]. Several proxies for the quality of health exist and can be divided into input and output indicators; the differences in access to physicians and hospital beds both are input indicators. Europe and Central Asia have 24.7 physicians per 10,000 people, South Asia 7.8, and Sub-Saharan Africa 1.9. The average number of hospital beds per 10,000 people is 58 in high human development countries, compared with 9 in medium human development countries and 13 in low human development countries [9•].

In summary, as it was shown, it is very complex to classify different regions or countries according to HD because HD is multifactorial, and very heterogenous. In addition, the data of poorer countries is limited. The last update of Human Development Indices and Indicators (the 2018 Statistical Update) published for the United Nations Development Program reflects human development progress over 1990–2017. After 28 years since the launch of the first human development report, we have a better integrated way to evaluate the human development [10]. It is important for health workers to know this integrated information in order to better understand publications from all over the world. The data discussed in this article come from several of these DC, and are compared, in some instances, with data from developed countries, mainly US.

Table 1 Developing countries according to human development indices [9]

Arab States (20 countries or territories)

Algeria, Bahrain, Djibouti, Egypt, Iraq, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, State of Palestine, Qatar, Saudi Arabia, Somalia, Sudan, Syrian Arab Republic, Tunisia, United Arab Emirates, Yemen.

East Asia and the Pacific (24 countries)

Cambodia, China, Fiji, Indonesia, Kiribati, Democratic People's Republic of Korea, Lao People's Democratic Republic, Malaysia, Marshall Islands, Federated States of Micronesia, Mongolia, Myanmar, Nauru, Palau, Papua New Guinea, Philippines, Samoa, Solomon Islands, Thailand, Timor-Leste, Tonga, Tuvalu, Vanuatu, Viet Nam.

Europe and Central Asia (17 countries)

Albania, Armenia, Azerbaijan, Belarus, Bosnia and Herzegovina, Georgia, Kazakhstan, Kyrgyzstan, Republic of Moldova, Montenegro, Serbia, Tajikistan, The former Yugoslav Republic of Macedonia, Turkey, Turkmenistan, Ukraine, Uzbekistan.

Latin America and the Caribbean (33 countries)

Antigua and Barbuda, Argentina, Bahamas, Barbados, Belize, Plurinational State of Bolivia, Brazil, Chile, Colombia, Costa Rica, Cuba, Dominica, Dominican Republic, Ecuador, El Salvador, Grenada, Guatemala, Guyana, Haiti, Honduras, Jamaica, Mexico, Nicaragua, Panama, Paraguay, Peru, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Suriname, Trinidad and Tobago, Uruguay, Venezuela.

South Asia (9 countries)

Afghanistan, Bangladesh, Bhutan, India, Islamic Republic of Iran, Maldives, Nepal, Pakistan, Sri Lanka.

Sub-Saharan Africa (46 countries)

Angola, Benin, Botswana, Burkina Faso, Burundi, Cabo Verde, Cameroon, Central African Republic, Chad, Comoros, Congo, Democratic Republic of the Congo, Côte d'Ivoire, Equatorial Guinea, Eritrea, Kingdom of Eswatini, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Mauritius, Mozambique, Namibia, Niger, Nigeria, Rwanda, São Tomé and Príncipe, Senegal, Seychelles, Sierra Leone, South Africa, South Sudan, United Republic of Tanzania, Togo, Uganda, Zambia, Zimbabwe.

AML Epidemiologic Data in DC: Are They Different From Developed Countries?

Approximately 70% of deaths from cancer occur in low- and middle-income countries (LMIC) [11]. Late-stage presentation and inaccessible diagnosis and treatment are common in these regions [12•]. In 2015, only 35% of low-income countries reported having pathology services generally available to the public sector. More than 90% of high-income countries reported that treatment services are available, compared with less than 30% of LMIC [12•]. Only 1 in 5 LMIC have the necessary data to drive cancer policy [12•] The GDP of all the high-income countries in 2010 was 45.2 trillion US dollars compared with 20.4 trillion US dollars for the GDP of all the middle-income countries and 0.3 trillion US dollars for the low-income countries [12•]. Overall, high-income regions spend 5–10 times more on cancer control on a per capita basis than LMIC [12•]. Concerning access to the new treatments, the gap between high-income countries and LMIC is increasing, especially since low-income countries must treat more frequently patients in advanced stages in which the great majority of the new drugs are registered [12•].

AML incidence rates in world populations generally ranged from 3.0 to 4.0 cases per 100,000 person-years in adult populations, with the highest incidence rates occurring in US, Europe, and Australia, while DC had about one-third the incidence of AML [1, 13].

The median age at diagnosis in DC has been observed 10 years earlier than in developed countries [14–17], with a mean age of 32–44 years compared with a median of 60–70 years in some developed countries like US or UK [1, 3].

The low incidence of AML in specific groups is showed in the US studies that found a higher frequency of acute lymphoblastic leukemia (ALL) in Latin American (LA) adults, in comparison with other ethnicities (Caucasian, Asian, African American) [1, 18–20]. Descriptive epidemiologic studies have reported a higher incidence of ALL in the LA population compared with other racial/ethnic groups [18]. For instance, in Mexico there is a slightly higher incidence of ALL than AML in the population over 16 years of age [18]. The origin of these differences in incidence and age is unclear. Socio-economic factors including the aging population in developed countries and reduced access to healthcare in elderly patients in developing countries could explain these variations [18]. Other factors including differences in genetics, molecular pathways, environmental exposition, and diet should be explored [18, 19].

Nevertheless, acute promyelocytic leukemia (APL) deserves attention because of the higher incidence observed in some developing DC. LA population living in the US have a greater frequency of APL compared with non-LA Caucasian population (24.3 vs 8.3%) and younger at presentation (31.5 vs 46 years) [20]. This finding has also been observed in other LA countries such as Mexico (35.5%) [18, 19], Brazil (28.2%) [21], Venezuela (27.8%), and Peru (22%) [22]. The geographic variation suggests a possible genetic predisposition or environmental exposures to specific risk factors. Other conditions such as obesity and dietary patterns have been linked to APL [23]. The distribution of the breakpoint cluster regions of the PML/RARa fusion gene has been shown to be different in Mexican patients with APL than in Caucasians and similar to those observed in Asians [24]; this observation suggests genetic differences in the features of PML, with a higher predisposition for this disease in Mexico or, alternatively, a protective effect of these differences in Caucasians. As a result of the increased prevalence of APL in LA, multicenter studies employing a simplified treatment of the disease have been conducted, with results like those obtained in other populations employing more complicated treatment schedules [25•].

APL is the AML subtype with the highest cure rate if it is treated with the best and timely treatment, so the negative impact of inappropriate therapy in DC is huge. It is also interesting that the prevalence of acute megakaryoblastic leukemia, the M7 variant of the FAB classification of AML, has also been described as more frequent in Mexicans than in Caucasians [26].

Economic Burden and Quality of Life in AML

Overall Costs of Acute Myeloid Leukemia

AML accounts for approximately 1.1% of new cancer cases each year in the United States [1]. Despite the relatively low incidence rate of AML compared with other cancers, the economic burden of AML to commercial insurers in the United States is substantial; total average costs were more than $300,000 per person year [27]. For patients with AML, the driving cost component is hospitalization-related costs during induction chemotherapy (IC) and hematopoietic stem cell transplantation (HSCT)-related costs [28••]. Even at centers where outpatient management after IC is available, readmissions are frequent and inpatient charges are rarely completely avoided [29]. In addition, intense outpatient monitoring, transfusion support, and antimicrobial prophylaxis are standard among those who achieve remission after IC or among patients receiving less aggressive treatments [30]. However, patients with AML who are not candidates for standard IC have different clinical profiles than those who are [31], and real-world assessments are needed for both younger and older patients with AML due to their different prognoses and profiles [32].

Although it can be difficult to make direct comparisons among studies because of methodologic differences, treatment approach, and variable costs across centers of care, they all show that AML is costly. AML drugs are comparable to other cancer drugs that tend to have higher cost-effectiveness thresholds than non-cancer medications [33]. Several potential explanations for this higher cost-effectiveness threshold for oncology medications have been suggested that include the greater severity of the disease, extended exclusivity protection, and a very narrow indication for a specific indication which creates a quasi-monopoly situation [33].

QoL and Psychological Considerations in AML

In addition to cost-effectiveness proper analysis, it is necessary better quality of life (QoL) studies because some of the most difficult challenges facing patients with AML and those treating and caring them are related to health-related quality of life (HRQoL) and psychosocial well-being [28••]. Systematic reviews have demonstrated that HIC is associated with an overall improvement in HRQoL despite an initial reduction associated with hospitalization. In patients with AML who are ineligible for HIC, HRQoL is compromised, and LIT has been shown to maintain, not improve HRQoL, indicating the need for new treatments which improve QOL as well as duration of survival in patients ineligible for HIC [30]. These studies have demonstrated that poorer HRQoL at diagnosis is associated with poor survival. [30]. The impact of treatment, either HIC, LIC, or SC, is heterogenous and depends on the time when it is measured. Further, QoL is a complex issue, scales are variable, and results differ from one study to another.

In the same way, several studies have shown the psychological burden of AML in both younger and older patients [28••, 30]. Due to the sudden onset and need to treat rapidly, patients with AML also reported feeling overwhelmed and had trouble processing the large quantity of information regarding their diagnosis and potential treatment options, which may have contributed to increases in psychological distress and feelings of helplessness [34]. In a recent publication, anxiety and depression are frequent in adult patients with AML and both predict unfavorable survival [35].

Further research is required to better understand the overall value of new treatments to both patients and healthcare providers as costs and HRQoL become increasingly important in the evaluation of new treatments [30].

Barriers to Access to Therapy in Developing Countries

As previously stated, the data in this report come from DC as defined in the HD Report [8]. Most of available information is derived from middle HDI countries because reliable information is very limited from low HD countries. The focus in this report is mainly LA population; nevertheless, the obstacles are similar in all DC. In these countries, we face several challenges and barriers for therapy access.

AML is not a common cancer, and it is a costly disease [27]. The large economic weight that AML demands affects not only the healthcare system at large but may also lead to financial hardship and high-stress burden among AML patients. AML affects mainly older adults over the age of sixty, and the treatment results until today are disappointing. This scenario, in DC with limited health resources, favors the health authorities to use their low budget preferentially in another illness that have higher incidence and a better chance to achieve higher social impact. Even among neoplastic disorders, leukemia is not as common as solid tumors and frequently more money is allocated to treat other types of more prevalent cancer. Sometimes the social impact of a relative higher number of survivors of solid tumors favors the health authorities to minimize the treatment of leukemias, mainly in older adults. Nevertheless, the median age of AML in DC is

strikingly different from that routinely reported in the literature from developed countries, and consequently, the economic impact on economically active population is larger.

Different studies have shown that socioeconomic factors (insurance, race, education, and occupation) are related with outcomes [36–39]. A large study in the US population, analyzing 2992 AML-patients, showed that education level (but not income) was associated with survival. Higher education in younger patients with AML was associated with a higher HSCT rate and a longer OS. Interestingly, the group of patients with a high-education level had a clear OS improvement in the most recent years, with the 5-year OS increasing from 39 to 58% (between 2000–2004 vs 2010–2014) in comparison with the group of patients with a low and medium education level with no improvements in the 5-year OS in the same period of time [40]. Conversely, a recently published study in France showed that in older AML-adults, socioeconomic status was not significantly associated with OS when adjusted with other prognostic factors [41].

The reported outcomes in DC are poor when compared with developed countries. A study from Brazil showed that AML-patients treated with intensive chemotherapy had a 5-year OS of 22% with an early mortality of 22% [42•]. In México, we recently showed the results of a multicenter experience of 525 adult-AML patients where the outcomes of patients treated with intensive chemotherapy are also inferior in comparison with developed countries with a 3-year OS of 34.8% and an early-mortality of 17.8% [43]. The high rate of induction-related mortality is very frequent in DC; it uses to be around 25% or as high as 39% in India [44, 45]. The main early-mortality cause in these reports was infection [42•, 43–45]. The post-induction outcome is poor as well, with an early high relapse rate, 43% at a median time of 7 months in Brazil [42•], and an overall survival of 42% at 1 year in India [44]. The number of patients rejecting treatment is high in DC, and the causes are multifactorial: advanced age; live further away from the hospital; lack of social support; concerned about toxicity to chemotherapy, apathy and fatalistic attitude, alternative medicine (homeopathy, herbalism); and mainly lack of financial support [44].

Results in the elderly patients are even worse. In a recent publication from India, from a total of 402 AML elderly patients (mean age 68 years) only 188 patients (46.7%) received either low-dose cytarabine (LDAC), hypomethylating agents, or best supportive care (BSC). The reported survival was 3.9, 6.4, and 1.2 months with LDAC, HMA, or BSC, respectively. The remaining patients, 213 (53.3%) refused care [46].

In AML, the single most important factor for not proceeding with treatment was lack of financial resources (81%). A small proportion of patients (22%) that did not opt for treatment in reference centers went on to receive IC from smaller facilities, but clearly, the vast majority did not receive further treatment and succumbed to their disease. Another frequent cause of rejecting treatment in DC is access to alternative medicine [44].

Delayed diagnosis may decrease the number of complete remissions (CR) mainly in younger patients when AML diagnosis to treatment is longer than only 5 days [47], the delay to receive treatment in DC is usually greater than 5 days, and it is not unusual that, at diagnosis, patients have an active infection.

Apart from leukemia high relapse deaths, infection is an important cause of mortality in DC. Infection not only jeopardizes survival but is the main cause of longer length of hospital stay. Because of the inappropriate conditions for AML treatment, higher incidence of bacterial and fungal infections is frequently reported. These inappropriate conditions could be associated to the tropical climate, lack of enough beds in rooms with positive-pressure laminar flow, and difficulties in the access to the workup for invasive mold disease [48]. Neutropenic fever (NF) is a very common complication during induction therapy and even after consolidation. In a real-world report from India, all patients developed NF during induction [44]. A big challenge is the increased incidence of multidrug resistant bacteria, recognized as a global phenomenon. Nevertheless, invasive fungal infections (IFI) are increasing and are responsible of at least one third of infections in acute leukemia. In some DC, like India, as much as 44% patients who died in induction had evidence of a possible or definitive IFI [44] which clearly exceeds rates reported in developed countries [49]. In a recent publication from Southeastern Asia, predisposing factors for IFI were shown in multivariate analysis: deep/prolonged neutropenia (> 30 days) and receipt of parenteral nutrition [50]. IFI incidence is magnified due to the limited resources to both the insufficient number of pathogen isolates and the restricted access to costly modern antifungal therapy.

On the other hand, health system coverage is very heterogeneous between DC. In comparison with some developed countries as the Nordic nations, where all the cancers are fully covered by a unique national health system, in some DC health systems are fragmented and the access is inequitable. For instance, in India, 85% of expenditure on health happens from noninsured, out-of-pocket spending and different treatment centers are likely to have diverse costing structures, based on whether they are private for-profit, private non-profit and fully or partly government subsidized hospitals. Similarly, it seems to be significant heterogeneity between hospitals with regard to diagnostic facilities available, allogeneic SCT facility, and access to trained personnel and supportive care [44]. Likewise, in México, 23.1% is treated in private medical services, 36.8% under social security (fractionated in different systems), and 40.1% has no insurance [51]. Patients with private insurances have access to all the diagnostic tests and new drugs, whereas patients with no insurance have a very limited access to both diagnostic tests and

drugs. In Brazil, according to data from 2012, most of hospitals (66%), hospital beds (70%), and specialized hospitals for AML treatment (87%) were private. In addition, 95% of diagnostic support and therapy establishments were owned by the private sector. Nevertheless, around 80% of the population still rely on the publicly funded healthcare system, which has major hurdles in AML successful treatment, including limited or no access to immunophenotyping, cytogenetic and molecular tests, drug unavailability and lack of beds for intensive chemotherapy, and delayed or no access to transplantation when indicated [42•].

Finally, the access to clinical trials is very limited in DC. Eight new drugs have been approved in the last 3 years for AML [52–60]. As we can see in Table 2, the clinical trials that led to the approval of these drugs were carried out mainly in developed countries [61]. Most of these drugs are not yet approved or available in many countries outside US and Europe. In the same way, the number of AML clinical trials registered in clinicaltrials.gov (recruiting or not yet recruiting) is very limited in DC (Table 3) [62].

In conclusion, the clinical course for adult patients with AML treated in DC points to significant disparities compared with developed countries; this difference lies in multifactorial reasons not only attributed to the disease per se but rather to socioeconomic factors and public health policies-related issues [42•]. It is also important to note that most of the data from DC refer to a "real world scenario," which is in sharp contrast to those commonly reported by clinical trials. In DC, treatment of patients with AML is substantially hampered by

the delayed start of induction chemotherapy (because of delayed diagnosis), drug unavailability, and lack of adequate infrastructure for chemotherapy and/or stem cell transplantation. A high proportion of patients reject treatment and the causes are multifactorial, but mainly, financial. To further complicate this scenario, not only there are barriers to afford the expensive direct and indirect costs of AML but diagnostic procedures like standard cytogenetic and molecular analyses are still not routinely performed in most institutions specialized in hematological malignancies treatment [42•]. In many DC, the biggest constraint is the cost of the treatment and the absence of a universal health security net to treat all patients with this diagnosis [44].

Possible Solutions

DC should aspire to have better human development; health is only part of a global well-being, and improving is only possible with better evaluation of the HDI and a global effort to achieve a more equitable wealth distribution. In the meantime, there are several ways to enhance the different problems that DC faced with new causes of morbidity and mortality, mainly thrombotic, and cancer diseases. This is the case of AML; as noted above, the first step should be to identify the main difficulties that are related with the poor outcomes of AML in DC. It is crucial that public health systems in these countries turn to a more efficient structure integrating the fragmented institutions and carry out more epidemiological studies to better understand how the disease characteristics interact with socioeconomic factors. This more appropriate health system would shorten the time from diagnosis to treatment and allow a better outcome of induction therapy. The interaction with developed countries could contribute to a more successful result in AML. An example is the report of the International Consortium on Acute Promyelocytic Leukemia (IC-APL) [25•]. Patients with APL in DC have significantly worse outcomes when compared with developed countries, mainly related with a high rate of early mortality. The main objective of the IC-APL was to create a network of institutions in DC that would share knowledge and data as well as receiving support from experts from US and Europe. The initiative included the standardization of diagnostic tests, treatment, and supportive care. This resulted in a decrease of almost 50% in early mortality and an improvement in OS of almost 30% compared with historical controls, resulting in similar OS to those reported in developed countries. The use of a cheaper anthracycline daunorubicin instead of idarubicin does not compromise these good results. Some of the lessons learned by this initiative were that establishing clinical networks involving developed and DC may be a very useful strategy. It favors simpler diagnosis methods, the implementation of national reference laboratories allowing training of laboratory personnel in new

Table 2 Recruiting and not yet recruiting clinical trials registered in clinicaltrials.gov for AML by country and the total country population. [61]

Country	AML clinical trials	Population
Developed countries		
US	396	327,167,434
Germany	231	82,927,922
Canada	197	37,058,856
France	66	66,987,244
Spain	47	46,723,749
Australia	31	24,992,369
Developing countries		
China	64	1,393,000,000
Russian Federation	17	144,478,050
Brazil	9	209,469,333
Turkey	6	82,319,724
Mexico	6	126,190,788
Argentina	3	44,494,502
Egypt	2	98,423,595
India	1	1,353,000,000

Table 3 Countries included in the clinical trials of new AML-drugs, by the World Bank classification [62]

Drug/study	High-income countries	Low and middle-income countries
Midostaurine, RATIFY NCT00651261 225 sites in 17 countries	Australia, Belgium, Canada, Czech Republic, France, Hungary, Germany, Italy, Israel, Netherlands, Slovakia, Spain, United Kingdom, US. (US + Canada: 176 sites)	Argentina, Brazil, Mexico, Russia
Gemtuzumab-ozogamicin ALFA-0701 NCT00927498 19 sites	France	
CPX351 NCT01696084 39 sites	Canada, US	
Enasidenib NCT01915498 24 sites	France, US	
Ivosidenib NCT02074839 24 sites	France, US	
Gilteritinib NCT02421939 127 sites	Belgium, Canada, France, Germany, Italy, Israel, Japan, Poland, Republic of Korea, Spain, Taiwan, United Kingdom, US.	Turkey
Glasdegib NCT01546038 81 sites	Canada, Germany, Italy, Poland, Spain, US	
Venetoclax NCT02203773 23 sites NCT02287233 9 sites	Australia, France, Germany US Australia, Germany, Italy, US	

technologies, and quality control routines as well as foster medical education by training clinical staff and creating exchange of experiences and guidelines [63]. This kind of collaboration could be extrapolated to other scenarios, for instance, reduce the higher morbidity and mortality rates from infection in AML through the implementation of better diagnostic methods that allowed more properly designed studies evaluating the bacterial and fungal epidemiology of each country.

In several DC, there are university facilities where the healthcare quality is usually better. In developed as in DC, academic centers mostly offer better patient security and reach major improving in healthcare quality [64, 65]. The influence of these academic centers can help to get better healthcare through teaching, guidelines, and even changing inappropriate healthcare policies.

Newer laboratory methods may allow DC to have access to modern laboratory techniques; for instance, the procedure of dried blood spots enable sending samples to reference laboratories in a cheaper way, for both mutation detection [66] and

more precise and rapid diagnosis of opportunistic infections [66, 67]. Likewise, the WHO has recently introduced the ASSURED standards for developing assays for low-resource areas [67]. These electricity-free systems and point of care devices would be of potential applicability.

One of the biggest obstacles to healthcare in low-resource settings is getting the patient to the clinic. This can be expensive at the onset, and if the travel takes several days, it can be economically untenable. Why not take the test to the patient? The isothermal methods, like LAMP (loop-mediated isothermal amplification), are promising. Studies using LAMP to detect the promyelocytic leukemia/retinoic acid receptor a transcript in acute promyelocytic leukemia reliably demonstrate the feasibility of isothermal PCR for rapid and simple diagnostics [68].

Another strategy is the use of telemedicine and mobile technology. An average annual growth rate of 1.9% between 2018 and 2025 will bring the total number of mobile subscribers to 5.8 billion (71% of the population). Of the 710 million people expected to subscribe to mobile services for

the first time over the next 7 years, half will come from the Asia Pacific region and just under a quarter will come from Sub-Saharan Africa [69]. There were preliminary reports on the use of telemedicine in hematology [70] and recent reports of the use of smartphone apps in cancer patients [71]. In addition, tumor board teleconferences could provide a valuable tool for continuing medical education in the management of AML and other malignancies [72]. Current COVID-19 pandemia had showed us the huge advantage of virtual academic teaching and the relevance of better telemedicine improvements.

Regarding novel drugs to treat AML, it is an exciting area for clinicians since the last 2 years, when we have an increasingly number of drugs to treat AML. Unfortunately, until today, several DC are far from the routine use of these drugs. The efforts of the past 18 years to provide access to TKI therapy to CML patients in low-middle income countries, the GIPAP (Glivec International Assistance Program) have shown us that it is possible to run a humanitarian access program for an oncology product, extending survival of patients in these countries and achieving overall survival close to that of patients in the western world. The experience also shows how the original impact of one original donor can foster an environment where other stakeholders are more likely to join the efforts [73].

While it would seem obvious that expensive pharmaceuticals would inevitably drive costs upward, actuality, a few unknowns exist [2•]. First, will these drugs provide "value" to the healthcare system and patients, a model which has traditionally considered the cost of achieving not only increased quantity but also quality of additional life? Second, will drugs that are more effective at getting patients into CR lead to a reduction in the costs accrued from transfusion support, hospitalizations, antibiotic use, and even the need for allo-HCT? And third, as many of the new drugs are given orally or with simplified administration schedules, will the reduced need for inpatient administration abate the cost associated with the drugs themselves? [2•].

It is therefore important to judge the cost-benefit of new AML treatments not only by the clinical benefit they may provide but also by how they will affect the downstream costs of AML care [2•]. Due to the novelty and lack of randomized trial data available for most of these drugs, very few budget impact and cost-effectiveness analyses are currently available [2•].

These assessments weigh the affordability and cost of a particular treatment not only against efficacy outcomes (i.e., remission rates, duration of remission, overall survival benefit) but also how achievement of these goals may translate to improvement in the quality of life and cost reduction by leading to symptom relief and treatment-free intervals [2•]. For AML, the ultimate economic value of new drugs will be determined by these variables in addition to considering the larger, but perhaps more indirect impact they may have on the use of healthcare resources [2•].

If these analyses prove that novel drugs have a better cost-effectiveness and they improve the quality of life and indirect costs of AML, certainly they are a better treatment also for DC. The availability of these drugs then be reinforced because they will save resources in DC as well.

Finally, the inclusion of more patients from DC in clinical trials will allow them to access new drugs earlier and allows these regions to discover if there are differences in efficacy or toxicity from a more global perspective.

Conclusions

AML is a costly disease anywhere. In DC the costs are higher as well, but results are poorer. Nevertheless, DC is a name designation that is frequently misunderstood. It is crucial to better understand the human development metrics in order to have a more properly evaluation of the socioeconomic scenario of each DC. Indeed, the main barrier in AML is lack of financial resources, but epidemiological data in DC are critical not only to achieve better knowledge of the health structure of each country and change public health structures and policies, but to manage the causes that impact in the poorer results of treatment, like delayed diagnosis, high early mortality, rejecting therapy, high prevalence of infections, and better access to transplant as well. The interaction with developed countries, like the IC-APL, would contribute to a more successful treatment results in AML. The contribution of technology with simpler and cheaper diagnostic methods as well as telemedicine is another aid. Finally, novel oral and targeted drugs that are now approved and available in developed countries might be of significant value in DC if they could be affordable by AML patients in these regions.

Compliance with Ethical Standards

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1.   Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018;68:7–30. https://doi.org/10.3322/caac.21442.

2.• Vaughn JE, Shankaran V, Walter RB. Trends in clinical benefits and costs of novel therapeutics in AML: at what price does progress come? Curr Hematol Malignancy Rep. 2019;14:171–8. https://doi.org/10.1007/s11899-019-00510-2. **This study analyzes the complexities of assessing costs versus benefits of AML treatment, emphasizing novel agents.**

3. Noone AM, Howlader N, Krapcho M, et al. SEER cancer statistics review, 1975–2015. Bethesda, MD: National Cancer Institute; 2018. based on November 2017 SEER data submission, posted to the SEER web site, April 2018. Available from: https://seer.cancer.gov/csr/1975_2015/.

4. Bewersdorf JP, Shallis RM, Wang R, Huntington SF, Perreault S, Ma X, et al. Healthcare expenses for treatment of acute myeloid leukemia. Expert Rev Hematol. 2019;12:641–50. https://doi.org/10.1080/17474086.2019.1627869.

5. Wang R, Zeidan AM, Halene S, Xu X, Davidoff AJ, Huntington SF, et al. Health care use by older adults with acute myeloid leukemia at the end of life. J Clin Oncol. 2017;35:3417–24. https://doi.org/10.1200/JCO.2017.72.7149.

6. National Cancer Institute. Drugs approved for acute myeloid leukemia. https://www.cancer.gov/about-cancer/treatment/drugs/leukemia#3.

7. Mahmoud D, Skikne BS, Kucmin-Bemelmans I, Alleman C, et al. Overall economic burden of total treatment costs in acute myeloid leukemia throughout the course of the disease. [abstract]. Blood. 2012;120:3614.

8. Giebe SL, Labopin M, Ehninger G, Beelen D, Blaise D, Ganser A, et al. Association of Human Development Index with rates and outcomes of hematopoietic stem cell transplantation for patients with acute leukemia. Blood. 2010;116:122–8. https://doi.org/10.1182/blood-2010-01-266478.

9.• UNDP. 2018. 2018 Statistical update: human development indices and indicators. New York. http://hdr.undp.org/en/content/human-development-indices-indicators-2018-statistical-update. Accessed December 12th, 2019. **An up-to-date UNDP document that evaluates new human development indices in both developed and developing countries.**

10. http://hdr.undp.org/en/2019-report. Accessed December 21, 2019.

11. Farmer P, Frenk J, Knaul FM, Shulman LN, Alleyne G, Armstrong L, et al. Expansion of cancer care and control in countries of low and middle income: a call to action. Lancet. 2010;376:1186–93. https://doi.org/10.1016/S0140-6736(10)61152-X.

12.• Todorovic V, Aapro M, Pavlidis N, Arsovski O, Belkacemi Y, Babovic N, et al. AROME-ESO Oncology Consensus Conference: access to cancer care innovations in countries with limited resources. Association of Radiotherapy and Oncology of the Mediterranean Area (AROME–Paris) and European School of Oncology (ESO – Milan). J BUON. 2019;24:2180–97. **A consensus document with the objective to prioritize the access to treatments and innovations in the most common types of cancer in low-middle income Mediterranean countries.**

13. Hagiwara M, Sharma A, Chung KC, Delea TE. Healthcare resource utilization and costs in patients with newly diagnosed acute myeloid leukemia. J Med Econ. 2018;21:1119–30. https://doi.org/10.1080/13696998.2018.1513847.

14. Jaime-Perez JC, Brito-Ramirez AS, Pinzon-Uresti MA, Gutierrez-Aguirre H, Cantu-Rodriguez OG, Herrera-Garza JL, et al. Characteristics and clinical evolution of patients with acute myeloblastic leukaemia in northeast Mexico: an eight-year experience at a university hospital. Acta Haematol. 2014;132:144–51. https://doi.org/10.1159/000356794.

15. Padilha SL, Souza EJ, Matos MC, Domino NR. Acute myeloid leukaemia: survival analysis of patients at a university hospital of Parana. Rev Bras Haematol Hemoter. 2015;37:21–7. https://doi.org/10.1159/000491989.

16. Meng CY, Noor PJ, Ismail A, Ahid MF, Zakaria Z. Cytogenetic profile of de novo acute myeloid leukaemia patients in Malaysia. Int J Biomed Sci. 2013;9:26–32.

17. Bahl A, Sharma A, Raina V, Kumar L, Bakhshi S, Gupta R, et al. Long-term outcomes for patients with acute myeloid leukaemia: a single center experience from AIIMS, India. Asia Pac J Clin Oncol. 2015;11:242–52. https://doi.org/10.1111/ajco.12333.

18. Colunga-Pedraza PR, Gomez-Cruz GB, Colunga-Pedraza JE, Ruiz-Argüelles GJ. Geographic hematology: some observations in Mexico. Acta Haematol. 2018;140:114–20. https://doi.org/10.1159/000491989.

19. Gomez-Almaguer D, Marcos-Ramirez ER, Montano-Figueroa EH, Ruiz-Arguelles GJ, Best-Aguilera CR, Lopez-Sanchez MD, et al. Acute leukaemia characteristics are different around the world: the Mexican perspective. Clin Lymphoma Myeloma Leuk. 2017;17:46–51. https://doi.org/10.1016/j.clml.2016.09.003.

20. Douer D, Preston-Martin S, Chang E, Nichols PW, Watkins KJ, Levine AM. High frequency of acute promyelocytic leukaemia among Latinos with acute myeloid leukaemia. Blood. 1996;87:308–13. https://doi.org/10.1182/blood.V87.1.308.308.

21. Rego EM, Jacomo RH. Epidemiology and treatment of acute promyelocytic leukaemia in latin america. Mediterr J Haematol Infect Dis. 2011;3:e2011049.

22. Otero JC, Santillana S, Fereyros G. High frequency of acute promyelocytic leukaemia among Latinos with acute myeloid leukaemia. Blood. 1996;88:377. https://doi.org/10.1182/blood.V88.1.377a.377a.

23. Li S, Chen L, Jin W, Ma X, Ma Y, Dong F, et al. Influence of body mass index on incidence and prognosis of acute myeloid leukaemia and acute promyelocytic leukaemia: a metaanalysis. Sci Rep. 2017;7:17998. https://doi.org/10.1038/s41598-017-18278-x.

24. Ruiz-Arguelles GJ, Garces-Eisele J, Reyes-Nunez V, Gomez-Rangel JD, Ruiz-Delgado GJ. More on geographic haematology: the breakpoint cluster regions of the PML/RAR alpha fusion gene in Mexican mestizo patients with promyelocytic leukaemia are different from those in Caucasians. Leuk Lymphoma. 2004;45:1365–8. https://doi.org/10.1080/10428190310001657344.

25.• Rego EM, Kim HT, Ruiz-Argüelles GJ, Undurraga MS, Uriarte M, del Rosario Uriarte R, et al. Improving acute promyelocytic leukemia (APL) outcome in developing countries through networking, results of the International Consortium on APL. Blood. 2013;121(11):1935–43. https://doi.org/10.1182/blood-2012-08-449918. **Describe the procedure of this initiative in some developing countries to reach better results in the management of APL.**

26. Ruiz-Arguelles GJ, Marin-Lopez A, Lobato-Mendizabal E, Ruiz-Arguelles A, Nichols WL, Katzman JA. Acute megakaryoblastic leukaemia: a prospective study of its identification and treatment. Br J Haematol. 1986;62:55–63 doi.org/dpfwg6.10.

27. Hagiwara M, Sharma A, Chung KC, Delea TE. Burden of acute myeloid leukemia (AML) in a U.S. commercially insured population. *J Clin Oncol*. 2017;35(15(suppl)):e18330. https://doi.org/10.1080/13696998.2018.1513847.

28.•• Wiese M, Daver N. Unmet clinical needs and economic burden of disease in the treatment landscape of acute myeloid leukemia. Am J Manag Care. 2018;24(1Suppl):S347–55. **A comprehensive review of the current treatment aspects of AML, including management, economic burden and unmet patient needs**.

29. Vaughn JE, Othus M, Powell MA, Gardner KM, Rizzuto DL, Hendrie PC, et al. Resource utilization and safety of outpatient management following intensive induction or salvage chemotherapy for acute myeloid leukemia or myelodysplastic syndrome: a nonrandomized clinical comparative analysis. JAMA Oncol. 2015;1:1120–7. https://doi.org/10.1001/jamaoncol.2015.2969.

30. Bosshard R, O'Reilly K, Ralston S, Chadda S, Cork D. Systematic reviews of economic burden and health-related quality of life in

patients with acute myeloid leukemia. Cancer Treat Rev. 2018;69: 224–32. https://doi.org/10.1016/j.ctrv.2018.07.005.

31. Thomas X, Le Jeune C. Treatment of elderly patients with acute myeloid leukemia. Curr Treat Options in Oncol. 2017;18:1–16. https://doi.org/10.1007/s11864-017-0445-5.

32. Stein EM, Bonifacio G, Latremouille-Viau D, Guerin A, Shi S, Gagnon-Sanschagri P, et al. Treatment patterns, healthcare resource utilization, and costs in patients with acute myeloid leukemia in commercially insured and medicare populations. J Med Econ. 2018;21:556–63. https://doi.org/10.1080/13696998.2018.1425209.

33. Bae YH, Mullins CD. Do value thresholds for oncology drugs differ from nononcology drugs? J Manag Care Spec Pharm. 2014;20:1086–92. https://doi.org/10.18553/jmcp.2014.20.11.1086.

34. LeBlanc TW, Fish LJ, Bloom CT, et al. Patient experiences of acute myeloid leukemia: a qualitative study about diagnosis, illness understanding, and treatment decision-making. Psychooncology. 2017;26(12):2063–8. https://doi.org/10.1002/pon.4309.

35. Ding T, Wang X, Fu A, Xu L, Lin J. Anxiety and depression predict unfavorable survival in acute myeloid leukemia patients. Medicine. 2019;98:e17314. https://doi.org/10.1097/MD.0000000000017314.

36. Byrne MM, Halman LJ, Koniaris LG, Cassileth PA, Rosenblatt JD, Cheung MC. Effects of poverty and race on outcomes in acute myeloid leukemia. Am J Clin Oncol. 2011;34:297–304. https://doi.org/10.1097/COC.0b013e3181dea934.

37. Bradley CJ, Dahman B, Jin Y, Shickle LM, Ginder GD. Acute myeloid leukemia: how the uninsured fare. Cancer. 2011;117: 4772–8. https://doi.org/10.1002/cncr.26095.

38. Sekeres MA, Peterson B, Dodge RK, Mayer RJ, Moore JO, Lee EJ, et al. Differences in prognostic factors and outcomes in African Americans and whites with acute myeloid leukemia. Blood. 2004;103:4036–42. https://doi.org/10.1182/blood-2003-09-3118.

39. Kristinsson SY, Derolf AR, Edgren G, Dickman PW, Björkholm M. Socioeconomic differences in patient survival are increasing for acute myeloid leukemia and multiple myeloma in Sweden. J Clin Oncol. 2009;27:2073–80. https://doi.org/10.1200/JCO.2008.18.2006.

40. Østgård LSG, Nørgaard M, Medeiros BC, Friis LS, Schoellkopf C, Severinsen MT, et al. Effects of education and income on treatment and outcome in patients with acute myeloid leukemia in a tax-supported health care system: a national population-based cohort study. J Clin Oncol. 2017;35(32):3678–87. https://doi.org/10.1200/JCO.2017.73.6728.

41. Berger E, Delpierre C, Despas F, Bertoli S, Bérard E, Bombarde O, et al. Are social inequalities in acute myeloid leukemia survival explained by differences in treatment utilization? Results from a French longitudinal observational study among older patients. BMC Cancer. 2019;19(1):883. https://doi.org/10.1186/s12885-019-6093-3.

42.• Benicio MTL, Ribeiro AFT, Américo AD, Furtado FM, Glória AB, Lima AS, et al. Evaluation of the European LeukemiaNet recommendations for predicting outcomes of patients with acute myeloid leukemia treated in low- and middle-income countries (LMIC): a Brazilian experience. Leuk Res. 2017;60:109–14. https://doi.org/10.1016/j.leukres.2017.07.005. **A comprehensive document that shows the poorer results of ELN recommendations in low-middle outcome nation like Brazil.**

43. Demichelis R, Zapata N, Leyto F, Terreros E, Carrillo A, Montaño E, et al. Survival analysis of adult patients with acute myeloid leukemia (AML) treated with intensive chemotherapy: results of a Mexican national AML registry. Clin Lymphoma Myeloma Leuk. 2019;19(1):S209–10. https://doi.org/10.1016/j.clml.2019.07.074.

44. Philip C, George B, Ganapule A, Korula A, Jain P, Alex AA, et al. Acute myeloid leukaemia: challenges and real world data from

India. Br J Haematol. 2015;170:110–7. https://doi.org/10.1111/bjh.13406.

45. Jacob S, Jacob SE, Suryanarayana BS, Dutta TK. Clinical profile and short term outcome of adult patients with acute myeloid leukemia. Indian J Hematol Blood Transfus. 2019;35(3):431–6. https://doi.org/10.1007/s12288-018-1051-9.

46. Govind BK, Chethan R, Lakshmaiah KC, Lokanatha D, Linu AJ, Suresh BMC, et al. Treatment patterns and comparative analysis of non-intensive regimens in elderly acute myeloid leukemia patients—a real-world experience from India. Ann Hematol. 2019;98:881–8. https://doi.org/10.1007/s00277-019-03600-6.

47. Sekeres MA, Elson P, Kalaycio ME, Advani AS, Copelan EA, Faderl S, et al. Time from diagnosis to treatment initiation predicts survival in younger, but not older, acute myeloid leukemia patients. Blood. 2009;113:28–36. https://doi.org/10.1182/blood-2008-05-157065.

48. Garnica M, Sinhorelo A, Madeira L, Portugal R, Nucci M. Diagnostic-driven antifungal therapy in neutropenic patients using the D-index and serial serum galactomannan testing. Braz J Infect Dis. 2016;20:354–9. https://doi.org/10.1016/j.bjid.2016.04.007.

49. Neofytos D, Lu K, Hatfield-Seung A, Blackford A, Marr KA, Treadway S, et al. Epidemiology, outcomes, and risk factors of invasive fungal infections in adult patients with acute myelogenous leukemia after induction chemotherapy. Diagn Microbiol Infect Dis. 2013;75(2):144–9. https://doi.org/10.1016/j.diagmicrobio.2012.10.001.

50. Lien MY, Chia-Hui C, Ching-Chan L, Li-Yuan B, Chang-Fang C, Su-Peng Y, et al. Epidemiology and risk factors for invasive fungal infections during induction chemotherapy for newly diagnosed acute myeloid leukemia: a retrospective cohort study. PLoS ONE. 13(6):e0197851. https://doi.org/10.1371/journal.pone.0197851.

51. https://www.inegi.org.mx/temas/derechohabiencia/ entered on Dec 1, 2019.

52. Stone RM, Mandrekar SJ, Sanford BL, Laumann K, Geyer S, Bloomfield CD, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. N Engl J Med. 2017;377:454–64. https://doi.org/10.1056/NEJMoa1614359.

53. Lambert J, Pautas C, Terré C, Raffoux E, Turlure P, Caillot D, et al. Gemtuzumab ozogamicin for de novo acute myeloid leukemia: final efficacy and safety updates from the open-label, phase III ALFA-0701 trial. Haematologica. 2019;104(1):113–9. https://doi.org/10.3324/haematol.2018.188888.

54. Lancet JE, Uy GL, Cortes JE, Newell LF, Lin TL, Ritchie EK, et al. CPX-351 (cytarabine and daunorubicin) liposome for injection versus conventional cytarabine plus Daunorubicin in older patients with newly diagnosed secondary acute myeloid leukemia. J Clin Oncol. 2018;36(26):2684–92. https://doi.org/10.1200/JCO.2017.77.6112.

55. Stein EM, DiNardo CD, Pollyea DA, Fathi AT, Roboz GJ, Altman JK, et al. Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia. Blood. 2017;130(6):722–31. https://doi.org/10.1182/blood-2017-04-779405.

56. DiNardo CD, Stein EM, de Botton S, Roboz GJ, Altman JK, Mims AS, et al. Durable remissions with Ivosidenib in IDH1-mutated relapsed or refractory AML. N Engl J Med. 2018;378(25):2386–98. https://doi.org/10.1056/NEJMoa1716984.

57. Perl AE, Martinelli G, Cortes JE, Neubauer A, Berman E, Paolini S, et al. Gilteritinib or chemotherapy for relapsed or refractory FLT3-mutated AML. N Engl J Med. 2019;381(18):1728–40. https://doi.org/10.1056/NEJMoa1902688.

58. Cortes JE, Heidel FH, Hellmann A, Fiedler W, Smith BD, Robak T, et al. Randomized comparison of low dose cytarabine with or without glasdegib in patients with newly diagnosed acute myeloid leukemia or high-risk myelodysplastic syndrome. Leukemia. 2019;33(2):379–89. https://doi.org/10.1038/s41375-018-0312-9.

59. DiNardo CD, Pratz K, Pullarkat V, Jonas BA, Arellano M, Becker PS, et al. Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia. Blood. 2019;133(1):7–17. https://doi.org/10.1182/blood-2018-08-868752.

60. Wei AH, Strickland SA Jr, Hou JZ, Fiedler W, Lin TL, Walter RB, et al. Venetoclax combined with low-dose cytarabine for previously untreated patients with acute myeloid leukemia: results from a phase Ib/II study. J Clin Oncol. 2019;37(15):1277–84. https://doi.org/10.1200/JCO.18.01600.

61. https://data.worldbank.org/country. Entered on Dec 1. 2019.

62. https://clinicaltrials.gov/ct2/home. Entered on Dec 1, 2019.

63. Correa de Araujo Koury L, Ganser A, Berliner N, Rego EM. Treating acute promyelocytic leukaemia in Latin America: lessons from the international consortium on acute Leukaemia experience. Br J Haematol. 2017;177:979–83. https://doi.org/10.1111/bjh.14589.

64. Aljuaid M, Mannan F, Chaudhry Z, Rawaf S, Majeed A. Quality of care in university hospitals in Saudi Arabia: a systematic review. BMJ Open. 2016;6:e008988. https://doi.org/10.1136/bmjopen-2015-008988.

65. Mort E, Bruckel J, Donelan K, Paine L, Rosen M, Thompson D, et al. Improving health care quality and patient safety through peer-to-peer assessment: demonstration project in two academic medical centers. Am J Med Qual. 2017;32:472–9. https://doi.org/10.1177/1062860616673709.

66. Sala Torra O, Beppu L, Smith JL, Welden L, Georgievski J, Gupta K, et al. Paper or plastic? BCR-ABL1 quantitation and mutation detection from dried blood spots. Blood. 2016;127:2773–4. https://doi.org/10.1182/blood-2015-12-689059.

67. Drain PK, Hyle EP, Noubary F, Freedberg KA, Wilson D, Bishai WR, et al. Diagnostic point-of-care tests in resource-limited settings. Lancet Infect Dis. 2014;14(3):239–49. https://doi.org/10.1016/S1473-3099(13)70250-0.

68. Hashimoto Y, Hatayama Y, Kojima N, Morishita S, Matsumoto S, Hosoda Y, et al. Development of reverse transcription loop-mediated isothermal amplification for simple and rapid detection of promyelocytic leukemia-retinoic acid receptor a mRNA. Yonago Acta Med. 2016;59(4):262–9.

69. https://www.gsmaintelligence.com/research/ Accessed Jan 7, 2020.

70. Leymarie V, Flandrin G, Noguera ME, Leymarie F, Lioure B, Daliphard S, et al. Telehematology: a pilot experience of cytological diagnosis of acute myeloid leukemia via the Internet. A GOELAMS study. Haematologica. 2006;91:1285–6.

71. Mehdizadeh H, Asadi F, Mehrvar A, Nazemi E, Emami H. Smartphone apps to help children and adolescents with cancer and their families: a scoping review. Acta Oncol. 2019;58(7):1003–14. https://doi.org/10.1080/0284186X.2019.1588474.

72. Abu Arja MH, Stanek JR, Morales La Madrid AE, Lassaletta A, Bartels U, Qaddoumi I, et al. The Latin American brain tumor board teleconference: results of a web-based survey to evaluate participant experience utilizing this resource. Childs Nerv Syst. 2019;35(2):257–65. https://doi.org/10.1007/s00381-018-4000-x.

73. Malhotra H, Radich J, Garcia-Gonzalez P. Meeting the needs of CML patients in resource-poor countries. ASH Educ Program. 2019:433–42.