Monitoring asparaginase activity in middle-income countries

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Acute lymphoblastic leukaemia is the most frequent neoplasia in childhood with more than 85% of treated patients cured in high-income countries.[1] One of the key drugs in its treatment is L-asparaginase (ASNase). The activity of ASNase can be affected by different factors such as antibody production and different pharmacokinetics among formulations. Serum asparagine (Asn) deamination selectively eliminates leukaemia cells preserving normal cells, since normal cells have the ability to synthesise Asn intracellularly.[2,3] In order to ensure therapeutic benefit, it is necessary to measure ASNase activity, since different formulations and silent inactivation might exist (values below 0·1 IU/mL).[4] In 1996, Boos and colleagues[5] described that different ASNase preparations could have different half-lives and different initial concentrations, probably because of distinct *Escherichia coli* strains. Thus, it is important to be aware of the drug preparation and the substantial variability in interpatient response.

Since 2015, the Brazilian Sistema Único de Saúde (SUS, the Brazilian Health System) have provided ASNase for all oncological centres in the country. Aginasa (Medac, Kyowa, Japan) was distributed until early 2017, replaced afterwards by leuginase (Beijing SL Pharmaceutical, China). Subsequently, Zenatti and colleagues[6] showed that leuginase presented host-cell contaminating proteins and had lower plasma bioavailability in animals than did aginasa. These two facts happened when we were establishing a monitoring programme in our institution, to measure the pharmacokinetic differences between ASNase formulations.

Our initial aim was to implement the laboratory test to measure ASNase activity to improve supportive care in patients with acute lymphoblastic leukaemia in a reference centre in Southern Brazil. Samples were collected from 19 children and adults in our university hospital, between April, 2017, and December, 2017. ASNase activity in blood samples—taken before, 24h after, and 48h after each infusion—was measured as described previously and validated in a different centre in Brazil.[5] We analysed 262 serum samples taken 24h and 48 h after infusions. At the same dose and schedule, 60 (81%) of 74 samples of patients who received aginasa had an activity level of 0·1 IU/mL or more, but only five (3%) of 188 samples of patients who received leuginase showed ASNase activity of 0·1 IU/mL or more (χ^2 test, p<0·001). We then compared only samples collected 48 h after any intravenous infusion during induction and we observed a significant decrease in ASNase activity (χ^2 test, p<0·001) in samples from patients treated with leuginase, when compared with samples from patients who received aginasa. When we looked only at the first ASNase infusion, the median activity 48 h after infusion was 0·197 IU/mL in the aginasa group (n=7) compared with 0·03 IU/mL in the leuginase group (n=5; p=0·004). The figure shows ASNase concentrations during induction in three patients.

Importantly, in the 12-month follow-up, six patients died, five with active disease in the group that used only leuginase (n=10), four of them in first-line therapy. The mean time between diagnosis and death was 8 months. Our results highlight the importance of evaluating drug activity levels in patients during treatment of acute lymphoblastic leukaemia. Several reports[2,4] from European groups have indicated that monitoring ASNase activity is part of an adequate treatment, because different methods of administration, formulation, dose,

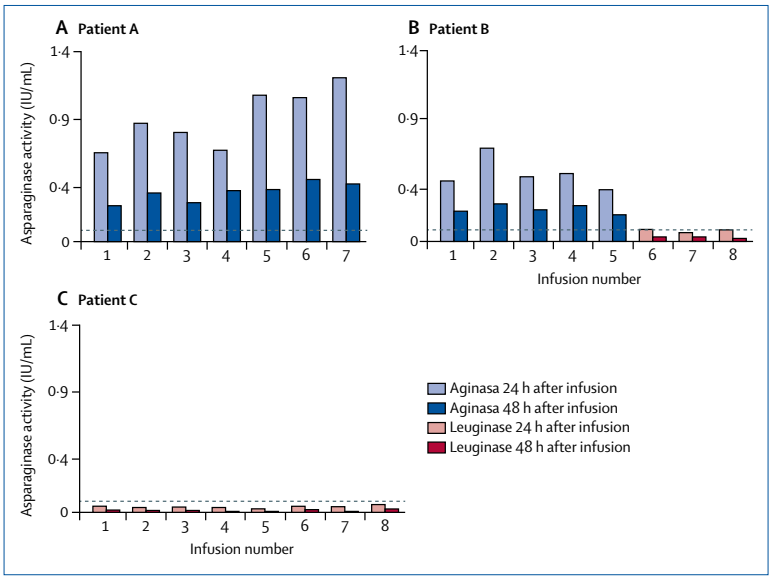

Figure: **ASNase concentrations during induction in three patients**
(A) Patient A received only aginasa and presented high activity in all samples. (B) Patient B received five infusions of aginasa and three infusions of leuginase, with a clear difference between the activity of the two drugs. (C) Patient C received only leuginase and never achieved the ideal activity, even after the first infusion, meaning that the low ASNase activity cannot be attributed to anti-asparaginase antibodies. The dotted line represents 0·1 IU/mL, ie, the silent inactivation level.

and immune responses could generate a substantial variability in ASNase activity, as well as in interpatient response. Since the monitoring of the biological activity of ASNase is not performed in Brazil, our study emphasises the relevance of following the international expert recommendations. Overall, these findings presented a worrisome scenario in which, despite our public health system following the best available protocol, patients might be at high risk of an undesired outcome. Our results can help policy makers to establish adequate strategies to provide efficient treatment for patients with acute lymphoblastic leukaemia.

These data are local but universal. Since many low-income and middle-income countries do not regularly monitor the quality and efficiency of antineoplastic drugs we wonder what is the expected impact on health.

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