SPOTLIGHT REVIEW ARTICLE

Back to the future: the amazing journey of the therapeutic anti-leukemia enzyme asparaginase *Erwinia chrysanthemi*

Wing H. Tong[1,2°] and Carmelo Rizzari[3,4]

[1]Department of Public Health and Primary Care (PHEG), Leiden University Medical Center, Leiden, The Netherlands; [2]Argos Zorggroep "DrieMaasStede", Center for Specialized Geriatric Care, Schiedam, The Netherlands; [3]Department of Pediatrics, Foundation IRCCS San Gerardo dei Tintori, Monza, Italy and [4]Department of Medicine and Surgery, University of Milano-Bicocca, Milano, Italy

°Current address: Evean "Oostergouw", Center for Specialized Geriatric Care, Zaandam, The Netherlands

Correspondence: W.H. Tong
w.h.tong@lumc.nl

Received: March 14, 2023.
Accepted: July 10, 2023.
Early view: July 20, 2023.

https://doi.org/10.3324/haematol.2022.282324

Abstract

For several decades, asparaginase has been considered world-wide as an essential component of combination chemotherapy for the treatment of childhood acute lymphoblastic leukemia (ALL). Discovered over 60 years ago, two main unmanipulated asparaginase products originated from primary bacteria sources, namely *Escherichia coli* and *Erwinia chrysanthemi*, have been available for clinical use. A pegylated product of the *Escherichia coli* asparaginase was subsequently developed and is now the main product used by several international co-operative groups. The various asparaginase products all display the same mechanism of action (hydrolysis of circulating asparagine) and are associated with similar efficacy and toxicity patterns. However, their different pharmacokinetics, pharmacodynamics and immunological properties require distinctive modalities of application and monitoring. *Erwinia chrysanthemi* asparaginase was initially used as a first-line product, but subsequently became a preferred second-line product for children who experienced immunological reactions to the *Escherichia coli* asparaginase products. An asparaginase product displaying the same characteristics of the *Erwinia chrysanthemi* asparaginase has recently been produced by use of recombinant technology, thus securing a preparation available for use as an alternative, or as a back-up in case of shortages, for the non-recombinant product. The long journey of the *Erwinia chrysanthemi* asparaginase product as it has developed throughout the last several decades has made it possible for almost every child and adult with ALL to complete the asparaginase-based protocol treatment when an immunological reaction has occurred to any *Escherichia coli* asparaginase product.

The various asparaginase products: mechanism of action and pharmacological properties

Asparaginase (ASNase) is a therapeutic enzyme used now for over 50 years as a component of multi-agent chemotherapy for children with ALL.[1-8] ASNase preparations available in the market mainly derive from the Escherichia coli (*E. coli*) and from the *Erwinia chrysanthemi* (*Erwinia c.*) strains,[9-14] display the same mechanism of action, have different pharmacokinetic (PK) and pharmacodynamic (PD) properties, and are available for clinical use in different forms: native *E. coli* and *Erwinia c.* products and the PEGylated *E. coli* product (PEG-ASNase) (Figure 1). ASNase mediates the breakdown of asparagine into aspartic acid and ammonia thus depleting the patient's bloodstream of the amino acid asparagine, which is indispensable for the leukemic blast metabolism, thus exploiting the metabolic weakness of leukemic blasts to autonomously produce asparagine, an amino acid important for the synthesis of several proteins.[15,16] In addition to asparagine (ASN) depletion, each ASNase product also results in a variable degree of glutaminase activity, whose significance remains partially unexplained and somewhat controversial. As an example, while Panosyan *et al*. found that deamination of glutamine (GLN) is a prerequisite for optimal ASN deamination by ASNases *in vivo*,[17] Chan *et al*. suggested, in contrast, that glutaminase-negative variants of ASNase would provide larger therapeutic indices than wild-type ASNase for asparagine synthetase (ASNS)-negative cancers.[18] Since GLN is the most abundant amino acid in the blood, its depletion under ASNase treatment is limited; however, a substantial reduction of

Drug	Initial FDA approval	Half-life (days)	Recommended dosing and interval	Recommended interval	Seminal EU / US trials
Native *E. coli* asparaginase	1978	IM: 1.3 IV: 17.3 - 19 hours (including recombinant variant)	6 000 IU/m^2	No more frequently than 3 times weekly	CCG- 101/143 CCG-1962 COALL-05-92 AIEOP ALL 2000 (NCT01117441) UKALL 2003 (NCT03911128)
Pegaspargase	1994	IM: 5.73 IV: 5.3	2 500 IU/m^2 for patients ≤ 21 years 2 000 IU/m^2 for patients > 21 years	No more frequently than every 14 days	DFCI 91-01 CCG-1962
Calaspargase pegol-mknl	2018	IM: NA IV: 13.4	2 500 IU/m^2 (only approved for patients ≤ 21 years)	No more frequently than every 21 days	COG AALL07P4 (NCT00671034) DFCI 11-001 (NCT01574274)
Asparaginase *Erwinia* chrysanthemi	2011	IM: 0.65 IV: 0.31	25 000 IU/m^2	3 times/week (M/W/F) for 6 doses	COG AALL07P2 (NCT00537030) DFCI 00-01 (NCT00165178) DFCI IV trial (NCT01643408)
Asparaginase *Erwinia* chrysanthemi (recombinant)-rywn	2021	IM: 0.76 IV: TBD	25 mg/m^2	Every 48 h (every 72-h dosing under investigation)	COG AALL1931 (NCT04145531)

Figure 1. Different asparaginase preparations used from 1970s onwards. Each preparation is accompanied by the following information: initial FDA approval, half-life (days), recommended dosing and interval, recommended interval and seminal EU/US trials. Adapted from Maese *et al.* Front Pediatr 2022.[62] IM; intramuscular; IV; intravenous; IU; international units; M/W/F: Monday, Wednesday, Friday schedule of dosing. The original NCT trials are available at: https://clinicaltrials.gov/.

blood GLN levels leads to extensive ammonia production and has been associated with ASNase-induced liver dysfunction and neurotoxicity. Since the glutaminase activity of the *Erwinia c.* ASNase is approximately five times higher than that of the *E. coli* ASNase products, it is important to consider such differences when investigating infusion-related and toxic side effects of the *Erwinia c.* ASNase products.[19,20] Also, it has been suggested that, although GLN is broken down to glutamic acid by ASNase, this may not necessarily lead to a high GLN depletion, as this amino acid can be supplemented from other organs *in vivo*.[21]

Native *E. coli* ASNase has a half-life of 1.24 days following an initial dose of 25,000 IU/m^2 (high dose ASNase, intramuscular [IM]), therefore multiple doses are necessary to attain prolonged and profound asparagine depletion.[22] In 1978, this preparation was authorized by the US Food and Drug Administration (FDA), but is currently no longer available in the United States for use in children under 18 years of age. Another paper reported that the half-life of native *E. coli* ASNase after an intravenous (IV) dose of 6,000 IU/m^2 is 17.3-19 hours.[23] In the 1970s, *Erwinia c.* ASNase was found to have PK characteristics similar to that of native *E. coli* ASNase, but with a shorter half-life of 0.65 days after IM administration.[22] In 2011, *Erwinia c.* ASNase (dosed at 25,000 IU/m^2) was approved by the FDA as a treatment option for ALL patients who experienced a hypersensitivity reaction (HSR) to *E. coli*-derived ASNase preparations.[13]

PEG-ASNase, a native *E. coli* ASNase product linked to polyethylene glycol (PEG), results in substantially prolonging the native *E. coli* ASNase half-life and reducing the associated hypersensitivity phenomena. PK and PD studies of PEG-ASNase began in the 1980s, and were usually conducted in patients who had HSR to native *E. coli* ASNase.[24-26] The half-life of PEG-ASNase given at 2,000 and 2,500 IU/m^2 was 357 +/- 243 hours (IV).[24] In 2006, based on a toxicity profile similar to that of the native *E. coli* ASNase and on a decreased incidence of antibody formation, the FDA approved PEG-ASNase for first-line use in patients with ALL.[27,28]

In 2008, the results of a study conducted in ALL children on a recombinant variant of native *E. coli* ASNase were reported by Pieters *et al*. They concluded that the recom-

binant and the native *E. coli* ASNase products were bioequivalent and had the same PD and toxicity profile.[29] This recombinant *E. coli* ASNase product is currently not available in the United States.

In 2018, the FDA approved a long-acting product similar to PEG-ASNase, namely calaspargase pegol-mknl (Cal-PEG).[30] This formulation used a different linker to *E. coli* ASNase, resulting in a longer half-life and shelf life. Patients treated with Cal-PEG every three weeks had a similar safety profile and event-free survival (EFS) to those treated with the traditional PEG-ASNase product.[30]

In 2021, based on the interim results of the COG AALL1931 trial study on the use of a recombinant *Erwinia c.* ASNase derived from a novel expression platform, the FDA approved its IM use at the dosage of 25 mg/m^2. In 2023, Maese *et al*. reported that this recombinant *Erwinia c.* ASNase was efficacious at 25/25/50 mg/m^2 when given IM on a Monday-Wednesday-Friday (MWF) schedule.[31] The use of this preparation resulted in a safety profile consistent with other ASNases that had earlier been approved by the FDA.

An interesting paper by Brigitha *et al*. recently evaluated how much ASNase is needed for optimal outcome in childhood ALL.[32] The authors concluded that: i) the level and duration of exposure have usually been based on the PK profile of the drug and on the assumption that a trough ASNase activity level of 100 U/L or greater is necessary to obtain a complete ASN depletion; ii) the level of exposure has not yet been associated with the outcome as long as the therapeutic level was reached. Authors also concluded that no clear cut-off for optimal exposure duration could be determined and that the achievement of this goal can also depend on immunophenotype, (cyto)genetic subgroups, risk group stratification, and backbone therapy.[32]

Clearly, the various ASNase products are not readily interchangeable and need to be used at specific schedules and doses. This is especially true for the *Erwinia c.* ASNase when it is used as second-line agent to replace the *E. coli* ASNase products when a clinically overt HSR or silent inactivation (SI) phenomena occurs.[2] Since several clinical studies have established the efficacy of *Erwinia c.* ASNase as a first- or second-line product, this specific aspect will be addressed later on in this Spotlight Review. Given that the incidence of *E. coli* ASNase and PEG-ASNase-associated HSR and SI are overall reported to be up to 60-70%, the importance of the availability of *Erwinia c.* ASNase is readily apparent.[33-39]

Erwinia c. asparaginase as first-line therapy: the journey starts

The benefits derived from an intensive use of any ASNase products, including the *Erwinia c.* ASNase, have been extensively reported. Table 1 shows all relevant clinical trials (including their main characteristics and relative results) where the *Erwinia c.* ASNase has been used as first-line product. Beginning in the 1990s, the UK Medical Research Council ALL consortium conducted a non-randomized trial comparing the toxicity of the *E. coli* and of the *Erwinia c.* ASNases given IM to a large cohort of ALL patients as first-line therapy.[40] Patients treated with *E. coli* ASNase had a significantly higher incidence of neurotoxicity, pancreatitis, and life-threatening sepsis than those receiving *Erwinia c.* ASNase. With a minimum follow-up of 4.5 years, the cohort of patients treated with the *Erwinia c.* ASNase had an outcome similar to that of patients treated with the native *E. coli* ASNase. This was the first study showing the efficacy of *Erwinia c.* ASNase when used as first-line therapy.[40]

Albertsen *et al*. studied the different patterns of ASN depletion between the IV and the IM administration route with the *Erwinia c.* ASNase given daily at 30,000 IU/m^2 for ten days during induction and twice weekly doses for two weeks during the re-induction phase of the NOPHO-92 ALL-protocol.[41] Over 92% of the treated patients had trough activity levels > 500 U/L[42,43] for both administration routes. Conversely, when the ASNase activity levels were evaluated during the re-induction, lower percentages of patients achieved the target level of > 100 U/L (almost 65% for the IV-treated children *vs.* 73% for the IM-treated children). The authors concluded that the *Erwinia c.* ASNase schedule adopted in the induction phase was unnecessarily intense, whereas it was insufficient for both administration routes in the re-induction phase.

In a national randomized study enrolling newly diagnosed patients in the AIEOP ALL-91 study, Rizzari *et al*. evaluated the therapeutic effects of the *Erwinia c.* ASNase product given IM to the subjects enrolled in the intermediate risk (IR) group of ALL either at weekly high doses, i.e., 25,000 IU/m^2, for a total of 20 doses over 20 weeks (experimental arm) during the reinduction and the early phase of maintenance or at standard doses, i.e., 10,000 IU/m^2, every 3-4 days for a total of four doses over two weeks, during the reinduction phase only (standard arm).[44] In this study, the results concerning outcome between the two arms were superimposable, thus proving that the *Erwinia c.* ASNase product given at standard doses and within a standard treatment schedule was capable of maintaining the outcomes expected from previous Berlin-Frankfurt-Münster (BFM)-based clinical trials using native *E. coli* ASNase.

A similar randomized study embedded in the same AIEOP ALL-91 study but designed for standard risk (SR) ALL patients was conducted in the frame of the IDH international co-operative effort named which included patients from Italy, Hungary and The Netherlands.[45] That study aimed to determine the efficacy of a BFM-type modified (i.e., less intensive) chemotherapy regimen including (experimental arm) or not (standard arm) a prolonged use of ASNase given at high doses (i.e., 25,000 IU/m^2, for a total of 20 doses over 20 weeks) at the beginning of the continuation

Table 1. Main findings reported in the studies featuring *Erwinia c*. ASNase given as first- or second-line product.

Study	Phase/dose/schedule/ administration route	Type of study	Patients	Outcome/main ASNase-associated findings	Ref.
MRC UK VIII ALL	Induction: *Erwinia C*. or *E. coli* ASNase given IM at 6,000 IU/m^2 3 x / week x 3 weeks	Non-randomized	483	5-year-DFS *Erwinia C. vs. E. coli* ASNase: 61% *vs*. 64% (NS)	Eden[40]
AIEOP ALL-95	Induction: *Erwinia C*. or *E. coli* ASNase 10,000 IU/m^2 given IV or IM q3 days x 8 doses	Non-randomized	62	Mean *Erwinia C*. ASNase activity levels: 130 U/L (IM) and 150 U/L (IV) Mean *E. coli* ASNase activity levels: 678 U/L (IM) and 553 U/L (IV)	Rizzari[58]
NOPHO-92 ALL	Induction: *Erwinia C*. ASNase 30,000 IU/m^2 given daily IV or IM x 10 days Re-induction: *Erwinia C*. ASNase 30,000 IU/m^2 2 x / week for 2 weeks; IV *vs*. IM	Non-randomized	40	Induction: mean *Erwinia C*. ASNase levels: 2,360 U/L (IV) and 1,710 U/L (IM) Re-induction: mean *Erwinia C*. ASNase levels: 110 U/L (IV) and 83 U/L (IM)	Albertsen[41]
AIEOP ALL-91	MR patients in re-induction and maintenance phase: *Erwinia C*. ASNase 25,000 IU/m^2 given IM weekly x 20 weeks (EXP) *vs*. 10,000 IU/m^2 given 2 x / week for 2 weeks (in reinduction only, SD)	Randomized	610	7-year-DFS EXP* *vs*. SD: 76% *vs*. 72% (NS)	Rizzari[44]
EORTC-CLG 58881	Induction: *Erwinia C. vs. E. coli* ASNase 10,000 IU/m^2 given IV 2 x / week x 4 weeks Re-induction: *Erwinia C. vs. E. coli* ASNase 10,000 IU/m^2 given IV 2 x / week x 2 weeks	Randomized	700	6-year-OS *Erwinia C. vs. E. coli* ASNase: 75% *vs*. 84% (*P*=0.002)	Duval[46]
I-BFM-SG (IDH-ALL-91)	SR patients in maintenance phase: *Erwinia C.* ASNase 25,000 IU/m^2 given IM weekly x 20 weeks (YES** *Erwinia C.* ASNase) *vs*. (NO** *Erwinia C.* ASNase)	Randomized	494	10-year-OS YES** *vs*. NO** *Erwinia C.* ASNase : 88% *vs*. 79% (*P*=0.03)	Pession[45]
NUH	Induction: *Erwinia C. vs. E. coli* ASNase 10,000 IU/m^2 given IM 2 x / week for 4 weeks	Non-randomized	116	*Erwinia C*. ASNase patients were 6.7 times more likely to have worse MRD (≥ 10-2) compared to *E. coli* ASNase patients (*P*=0.031)	Kwok[48]
CCG-1961	High-risk patients: first-line ASNase product in induction (standard BFM, standard duration): *E. coli* ASNase given at 6,000 IU/m^2, IM, 3 x week x 2 weeks *vs. E. coli* ASNase (3 x week x 4 weeks) standard, BFM increased duration Re-induction: augmented BFM arm PEG-ASNase 2,500 IU/m^2 given IM every 2 weeks x 6 *vs*. 10 Re-induction (routine shift as second-line): *Erwinia C*. ASNase 6,000 IU/m^2 given IM, 3 x / week for 2 weeks	Randomized	1,001	13 cases of 81 showed silent inactivation and had a significantly inferior outcome (*P*=0.031) at 30 months (not switched to *Erwinia C.* ASNase because SI was not detected in real time)	Panosyan[35]
DFCI 95-01	Re-induction: *Erwinia C. vs. E. coli* ASNase 25,000 IU/m^2 given IM weekly x 20 weeks	Randomized	491	5-year-EFS *Erwinia C. vs. E. coli* ASNase arms: 78% *vs*. 89% (*P*=0.01)	Moghrabi[47]

Continued on following page.

Study	Phase/dose/schedule/ administration route	Type of study	Patients	Outcome/main ASNase-associated findings	Ref.
AALL07P2***	Re-induction: PEG-ASNase 2,500 IU/m² given IV or IM every 2 weeks (frequency depending on risk stratification) Second-line (re-induction): *Erwinia C.* ASNase 25,000 IU/m² given IM 3 x / week for 2 weeks (to substitute for one PEG-ASNase dose)	Non-randomized	55	No EFS / OS data available Among samples collected during all courses: 96% of 48h samples and 85% of 72h *Erwinia C.* ASNase samples had trough activity levels > 0.1 IU/mL	Salzer[57]
DCOG ALL-10****	First-line ASP product and schedule in induction: *E. coli* ASNase 5,000 IU/m² given IV q 3 days x 8 doses Re-induction: PEG-ASNase 2,500 IU/m² given IV every 2 weeks x 15 Second-line product: Re-induction: *Erwinia C.* ASNase 20,000 IU/m² given IV 3 x / week for 2 weeks to substitute for one PEG-ASNase dose	Non-randomized	59	No EFS / OS data available Among samples during first two weeks of *Erwinia C.* ASNase: 96% of samples had at least one trough activity level > 0.1 IU/mL	Tong[21]
DFCI 00-01	Re-induction: *E. coli* ASNase ID arm, starting dose 12,500 IU/m² given IM weekly x 30 *vs.* *E. coli* ASNase FD, dose of 25,000 IU/m² given IM weekly x 30 As second-line: re-induction: *Erwinia C.* ASNase 25,000 IU/m² given IM 2 x / week to replace one *E. coli* ASNase weekly dose	Randomized	492†	5-year-EFS *E. coli* ASNase ID arm*****: 90% 5-year-EFS *E. coli* ASNase FD arm*****: 82% (*P*=0.04)	Vrooman[49]
AALL0331 and AALL0232	Re-induction: SR low PEG-ASNase 2,500 IU/m² given IV or IM every 2 weeks x 2 *vs.* SR low PEG-ASNase (same dose) and schedule: every 2 weeks x 6 Re-induction: HD MTX arm no PEG-ASNase *vs.* Capizzi MTX PEG-ASNase 2,500 IU/m² Second-line: re-induction: *Erwinia C.* ASNase 25,000 IU/m² given IM given IV or IM every 2 weeks x 2 3 x / week for 2 weeks to replace one PEG-ASNase dose	Randomized	(AALL0331) 5,195‡ (AALL0232) 3,001	10-year-DFS *Erwinia C.* ASNase (replacing PEG-ASNase): 86% 10-year-DFS PEG-ASNase (all doses): 86% 10-year-DFS missing PEG-ASNase doses: 77% (*P*=0.003)******	Gupta[51]
DCOG ALL-11****	Induction and re-induction: PEG-ASNase 1,500 IU/m² given IV every 2 weeks (N of doses depending on phase and risk stratification) As second-line: re-induction: *Erwinia C.* ASNase 20,000 IU/m² given IV 3 x week for 2 weeks to replace one PEG-ASNase dose	Non-randomized	37	During 1st 2 weeks of *Erwinia C.* ASNase treatment 76% of 48h samples and 24% of 72h samples had trough activity levels > 0.1 IU/mL	Kloos[50]

Continued on following page.

IM: intramuscular; IV: intravenous; DFS: disease-free survival; EFS: event-free survival; OS: overall survival; *Erwinia c.* ASNase: *Erwinia chrysanthemi* asparaginase; *E. coli* ASNase: native *E. coli* asparaginase; PEG-ASNase: pegylated *E. coli* asparaginase; ID: individualized dose; FD: fixed dose; NS: not significant; MRD: minimal residual disease; CTCAE: Common Terminology Criteria for Adverse Events; NUH: National University Hospital; h: hours. * EXP arm: experimental arm, *Erwinia c.* ASNase IM (25,000 IU/m^2) administered on weekly basis for 20 weeks trespassing to the continuation phase. SD arm: standard arm, *Erwinia c.* ASNase (10,000 IU/m^2) twice a week for 2 weeks during protocol II only. ** YES arm: arm including *Erwinia c.* ASNase IM (25,000 IU/m^2) administered on a weekly basis for 20 weeks during the continuation phase. NO arm: arm without any additional *Erwinia c.* ASNase during the continuation phase. ***** FD: administration of the *E. coli* ASNase at the fixed dose of 25,000 IU/m^2 (weekly) for a total 30 weeks. ID: administration of the native *E. coli* ASNase dose starting at 12,500 IU/m^2 (weekly) and individualized thereafter based on the results of the pharmacological monitoring (TDM). **** Induction starting with *E. coli* ASNase 5,000 IU/m^2 (eight doses q 3 days). Medium risk (MR) treated with PEG-ASNase 2,500 IU/m^2 (every two weeks, 15 doses in total). In case of hypersensitivity reaction (HSR), *Erwinia c.* ASNase (20,000 IU/m^2) was started. DCOG ALL-11 protocol: induction started with PEG-ASNase 1,500 IU/m^2 (every two weeks). TDM was applied and the dose of PEG-ASNase could be further lowered. In case of HSR, *Erwinia c.* ASNase (same dose) was started. *** *Erwinia c.* ASNase 25,000 IU/m^2 (Monday/Wednesday/Friday) schedule for 2 weeks. ****** Number of PEG-ASNase doses varied by trial and strata. Continuation phase did not contain any ASNase doses. †In Vrooman *et al.*,[63] 42 patients (out of 215 patients enrolled on DFCI protocol 00-01 between 2000-2002) received *Erwinia c.* ASNase IM. Twice-weekly *Erwinia c.* ASNase was well tolerated and achieved therapeutically effective trough activity levels in most native *E. coli* ASNase-allergic patients. It should be noted that the development of an allergy to native *E. coli* ASNase and subsequent switch to *Erwinia c.* ASNase did not adversely impact EFS.[63] ‡For AALL0232, data were also collected on whether patients receiving *Erwinia c.* subsequently discontinued it for any reason. Data on subsequent *Erwinia c.* continuation were not available for patients in AALL0331.

phase. In contrast to the previously described study conducted in IR patients, this randomized clinical trial, conducted in 355 SR ALL children, showed that, compared to the group receiving the standard treatment, the group receiving high-dose ASNase (*Erwinia c.*) for a protracted period of time (experimental arm) had a significantly increased 10-year disease-free survival (DFS) (87.5% *vs.* 78.7%) and a higher overall survival (OS) (93.7% *vs.* 88.6%). Of note, a 40% relative reduction (RR) in the risk of failure was achieved in the group of patients receiving the protracted high-dose ASNase (*Erwinia c.*) product, thus proving the beneficial effects of that product and schedule, in that chemotherapy context and in that subgroup of patients.[45]

Notwithstanding, two randomized clinical trials carried out in the same period (early-mid 1990s) in Europe by the European Organisation for Research and Treatment of Cancer (EORTC)[46] and in the US by the Dana-Farber Cancer Institute (DFCI) Consortium (Table 1)[47] showed that among ALL children (belonging to any risk group) randomly assigned to receive throughout the whole treatment schedule either the native *E. coli* ASNase or the *Erwinia c.* ASNase products (same dosage, administration route and treatment schedule), those treated with the *Erwinia c.* ASNase had consistently lower toxic effects but poorer EFS. These findings were mainly interpreted as secondary to an inadequate timing and dosage adopted for the *Erwinia c.* ASNase and therefore to a consequently inadequate asparagine depletion.

In 2006, Kwok *et al.* reported the results of their investigations on minimal residual disease (MRD) to compare the efficacy of *Erwinia c.* ASNase and native *E. coli* ASNase given IM at similar dosage and intervals during a classical four-drug induction therapy. They found that patients treated with the *Erwinia c.* ASNase were 6.7 times more likely to have higher MRD levels (≥ 10^{-2}) thus reflecting slower lymphoblast clearance, presumably due to insufficient ASNase activity.[48]

Both the therapeutic and toxic effects associated with the *Erwinia c.* ASNase used as front-line product may be either very similar or very different from those associated with the native *E. coli* ASNase products, greatly depending on the dosage and the schedule adopted.

Erwinia c. asparaginase as second-line therapy: the journey continues

After the first decade of its use, when *Erwinia c.* ASNase had mainly been used as a first-line ASNase with the findings previously reported, the efficacy of a switch to the *Erwinia c.* ASNase preparation after HSR to a native *E. coli* ASNase product became more evident and its use as second-line product became widespread.[1] Table 1 summarizes the most relevant details of the various clinical trials in which the *Erwinia c.* ASNase product has been used as second-line product. (See also below.)

The ASNase activity reduction found among the 280 high-risk pediatric ALL patients treated with *Erwinia c.* ASNase after HSR to a native *E. coli* ASNase had an impact on the outcome of the treated patients; in fact, Panosyan *et al.* found an increased rate of events among patients with Ab-positive titers detected during the interim maintenance-1 and the delayed intensification.[35] Also, Vrooman *et al.* showed that patients with SI occurring during treatment with native *E. coli* ASNase had a worse outcome when not switched to another ASNase product, whilst those with a HSR and switched to *Erwinia c.* ASNase fully maintained the expected outcome.[49]

In two further clinical studies conducted by the Dutch Childhood Oncology Group (DCOG), *Erwinia c.* ASNase was used as a second-line preparation. In the first study, Tong *et al.* studied ALL children presenting with either HSR or SI to PEG-ASNase during the intensification phase of ALL therapy and who were switched to *Erwinia c.* ASNase. Such a switch led to effective ASNase activity levels in

most patients.[21] In the second study, Kloos *et al*. studied the role of therapeutic drug monitoring (TDM) within the DCOG ALL-11 protocol.[50] After a HSR, 37 patients were started on *Erwinia c.* ASNase at 20,000 IU/m^2 (IV) three times a week for two weeks. During the two weeks, 76% had trough activity levels at 48 hours > 100 U/L but only 24% at 72 hours. Thereafter, the *Erwinia c.* ASNase product dose varied between 15,000 and 40,000 IU/m^2.[50] The main finding of that study was that, besides SI, also allergic-like reactions could be identified by using TDM.

Finally, the Children's Oncology Group (COG AALL0232) studied more than 3,000 patients with high-risk ALL comparing the outcome of patients receiving all the planned PEG-ASNase doses (group 1) with that of patients switched to receive the *Erwinia c.* ASNase to complete the planned ASNase treatment (group 2), and with that of patients who completely missed a variable number of ASNase doses, mainly, but not only, due to HSR (group 3). The authors found that the DFS was similar between groups 1 and 2, whilst in group 3, the DFS was inferior compared to group 1, with a HR of 1.5 (P=0.002).[51] The data showed that children with either HSR and/or SI occurring during the administration of *E. coli* ASNase consistently had a poorer outcome compared to those without such an immunological reactivity; when the *Erwinia c.* ASNase product was substituted for the *E. coli* ASNase, outcomes were maintained without unexpected additional toxicities.

Recombinant *Erwinia c.* ASNase product: is the future already here?

Despite the approval of the *Erwinia c.* ASNase as a second-line ASNase since 2011, important difficulties in the manufacturing process of *Erwinia c.* ASNase have occurred over the last two decades and this has led to global supply shortages of *Erwinia c.* ASNase.[52,53] For this reason, a recombinant *Erwinia c.* ASNase (namely JZP-458) utilizing a novel *Pseudomonas* fluorescent technology expression platform has recently been developed;[52] it has the same amino acid sequence as *Erwinia c.* ASNase and results in no immunologic cross-reactivity to *E. coli*-derived ASNase products. The recombinant technology-based production allows a stable and enhanced production process thus avoiding the supply problems with the non-recombinant *Erwinia c.* ASNase.

In 2021, in a phase I study conducted in healthy adult volunteers,[54] JZP-458 was used at a starting dose of 25 mg/m^2 (IM). Previously, it had been demonstrated that this formulation and dosage was similar in achieving sufficient ASNase activity when compared to the non-recombinant *Erwinia c.* ASNase (based on the dosage of 25,000 IU/m^2).[55] Lin *et al*. concluded that a single IM dose of JZP-458 (25 mg/m^2) resulted in similar ASNase activity levels compared to 25,000 IU/m^2 of the non-recombinant *Erwinia c.* ASNase.[54] In 2021, based on the clinical and pharmacological data derived from the studies described, the FDA granted the approval of JZP-458.[31]

In 2022, the results of a phase II/III study conducted within the AALL1931 protocol of the COG were published.[31] This study focused on the efficacy and safety of the recombinant *Erwinia c.* ASNase. Each scheduled dose of PEG-ASNase remaining after an HSR had occurred was replaced by six doses of JZP-458 given IM on a Mon/Wed/Fri basis. Maese *et al*. thoroughly studied three dosing regimens and concluded that JZP-458 given IM at 25/25/50 mg/m^2 on a Mon/Wed/Fri schedule was effective in ALL patients, thus supporting the conclusion that this product with such a dosage, schedule and administration route has an efficacy and a toxicity profile similar to that of the non-recombinant *Erwinia c.* ASNase, and also of the other ASNase preparations available for clinical use and applied at equivalent dosages. The IM use of the recombinant *Erwinia c.* ASNase is currently approved by the FDA but additional data deriving from the IV use are under evaluation.

As far as the preferred use of administration route is concerned, ASNase products should be given IV. In fact, the study by Place *et al*. showed that IV administration of PEG-ASNase was associated with similar outcomes and toxicity pattern but with decreased anxiety compared with IM native *E. coli* ASNase doses.[56] When focusing on the route of the native form of *Erwinia c.* ASNase, Tong *et al*. showed that the administration route might explain the higher median ASNase activity levels found by Salzer *et al*.[21,57] Of note, previous studies have shown that no differences in mean ASNase activity levels, ASN depletion, and ASNase antibodies were found after IV or IM administration of *Erwinia c.* ASNase.[41,43,58]

How best to choose and administer *Erwinia c.* ASNase products in the modern protocols?

Currently, the use of *Erwinia c.* ASNase is limited to the second-line setting and not to the first-line setting because of: i) the results of the previous (old) clinical trials; and ii) its PK characteristics which mandate the drug administration every 48 hour to maintain therapeutic ASNase activity levels ≥ 100 U/L, making it very difficult, if not impossible, to deliver the drug to cover the often several weeks-long ASN depletion needed to exploit its therapeutic efficacy. For example, a huge number of doses would be needed during the induction phase of the AIEOP-BFM ALL protocols (and of many others protocols) to achieve the 4 weeks-long ASN depletion needed.

Furthermore, when one considers also the current costs of *Erwinia c.* ASNase, its use in the first-line setting would be very expensive.[59] Therefore, the very few doses needed when PEG ASNase or the calaspargase products are used in the first-line setting make the use of these products the preferred option to be pursued.

Because of the recent frequent global shortages of the *Erwinia c.* ASNase, the recombinant form of *Erwinia c.* ASNase represents an opportunity to complement the market availability of the non-recombinant *Erwinia c.* ASNase preparation. This reassures physicians and parents on being able to complete any *E. coli* ASNase treatment in case of HSR or SI, and secures adequate opportunities of cure to ALL patients presenting with HSR or SI to the *E. coli* ASNase products.[60]

In the wider scenario of childhood ALL treatment, the currently available *Erwinia c.* ASNase products remain important drugs for the treatment of childhood ALL.[8] Even if a number of promising (and also quite expensive) new biological agents (such as blinatumomab and inotuzumab) are currently under investigation to show their efficacy and to deepen their acute and mid-/long-term toxicity profile, it seems quite difficult at the present time to foresee a time when ASNase products will be substituted by such targeted drugs in the short-medium term. Furthermore, some innovative *Erwinia c.* ASNase formulations aiming to improve its characteristics appear on the horizon, making it even more interesting to look towards the future of this important antileukemia agent.

Future directions

In this Spotlight Review, we have retraced the journey taken over the last six decades by the *Erwinia c.* ASNase, a chemotherapy agent particularly important for successfully replacing native or pegylated *E. coli* ASNase products when they were associated with clinically relevant HSR or SI.

The journey started by the *Erwinia c.* ASNase product in the 1970s has been characterized by the pioneering experiences conducted as a first-line ASNase preparation and, in more recent decades, as a second-line product after HSR and SI to *E. coli* ASNase products. Across the subsequent decades, the journey has also been characterized by a lack of continuity in its availability caused by flaws in the production process which, for the moment, seem to have been overcome. In any case, the new recombinant *Erwinia c.* ASNase product, currently available on the market, secures the continuous availability of this important drug.

The scientific knowledge accumulated over the decades on the pharmacology, biological characteristics and clinical use of the *Erwinia c.* ASNase today represents a very important asset to ensure that all children with ALL can be treated with the best dosage and schedule, and that they can attain the expected full benefit from any planned ASNase-based treatment programs.

Concluding reflections

The title of this Spotlight Review was intuitively derived from the 1985 American film directed by Robert Zemeckis "Back to the Future" starring Michael J. Fox and Christopher Lloyd, considered one of the greatest science-fiction films ever made. When both of us, as co-authors, were working on this scientific review of the *Erwinia c.* ASNase product, we came to realize even more, and even better, its long journey, marked by different events as far as its use (first- and second-line), schedules (including administration routes and dosages), manufacturing technologies (traditional and recombinant), and availability (shortages) have been concerned. And it somewhat resembled to us the "imaginary" journey made in that famous movie by the two leading actors with their time machine flying from the present to the past and then back to the future. But certainly, the "real" story of *Erwinia c.* ASNase is not yet over, and there is surely still more to come, just like all the sequels and adaptations made to the original movie after its first appearance in the cinemas.

Disclosures

CR has received reimbursement for travelling expenses and personal fees for scientific talks at scientific meetings sponsored by Servier, Jazz Pharmaceuticals, and Clinigen, companies involved in the production and marketing of different asparaginase products.

Contributions

WHT and CR performed the literature research and wrote the manuscript. CR supervised this Spotlight Review.

Acknowledgments

CR thanks the Comitato ML Verga for the unrestricted support to his clinical and research activities. He also thanks physicians, pharmacologists, nurses and technicians as well as parents and patients treated in his and AIEOP (Italian Association of Pediatric Hematology and Oncology) institutions for the contributions given to his research in the field of asparaginase. CR and WHT wish to thank Prof. Stephen Earl Sallan (Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA) for his accurate and selfless review of the text which greatly improved its final version.

References

1. Pieters R, Hunger SP, Boos J, et al. L-asparaginase treatment in acute lymphoblastic leukemia: a focus on Erwinia asparaginase. Cancer. 2011;117(2):238-249.
2. van der Sluis IM, Vrooman LM, Pieters R, et al. Consensus expert recommendations for identification and management of asparaginase hypersensitivity and silent inactivation. Haematologica. 2016;101(3):279-285.
3. Lanvers-Kaminsky C. Asparaginase pharmacology: challenges still to be faced. Cancer Chemother Pharmacol. 2017;79(3):439-450.
4. Salzer W, Bostrom B, Messinger Y, Perissinotti AJ, Marini B. Asparaginase activity levels and monitoring in patients with acute lymphoblastic leukemia. Leuk Lymphoma. 2018;59(8):1797-1806.
5. Baruchel A, Brown P, Rizzari C, et al. Increasing completion of asparaginase treatment in childhood acute lymphoblastic leukaemia (ALL): summary of an expert panel discussion. ESMO Open. 2020;5(5):e000977.
6. Rizzari C, Conter V, Starý J, Colombini A, Moericke A, Schrappe M. Optimizing asparaginase therapy for acute lymphoblastic leukemia. Curr Opin Oncol. 2013;25 Suppl 1:S1-9.
7. Asselin B, Rizzari C. Asparaginase pharmacokinetics and implications of therapeutic drug monitoring. Leuk Lymphoma. 2015;56(8):2273-2280.
8. Clavell LA, Gelber RD, Cohen HJ, et al. Four-agent induction and intensive asparaginase therapy for treatment of childhood acute lymphoblastic leukemia. N Engl J Med. 1986;315(11):657-663.
9. Figueiredo L, Cole PD, Drachtman RA. Asparaginase Erwinia chrysanthemi as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia who have developed hypersensitivity to E. coli-derived asparaginase. Expert Rev Hematol. 2016;9(3):227-234.
10. Keating GM. Asparaginase Erwinia chrysanthemi (Erwinaze®): a guide to its use in acute lymphoblastic leukemia in the USA. BioDrugs. 2013;27(4):413-418.
11. Maloney KW. Erwinia asparaginase: coming closer to an understanding of its use in pediatric acute lymphoblastic leukemia? Pediatr Blood Cancer. 2010;54(2):189-190.
12. Plourde PV, Jeha S, Hijiya N, et al. Safety profile of asparaginase Erwinia chrysanthemi in a large compassionate-use trial. Pediatr Blood Cancer. 2014;61(7):1232-1238.
13. Salzer W, Seibel N, Smith M. Erwinia asparaginase in pediatric acute lymphoblastic leukemia. Expert Opin Biol Ther. 2012;12(10):1407-1414.
14. Salzer WL, Asselin BL, Plourde PV, Corn T, Hunger SP. Development of asparaginase Erwinia chrysanthemi for the treatment of acute lymphoblastic leukemia. Ann N Y Acad Sci. 2014;1329:81-92.
15. Bussolati O, Belletti S, Uggeri J, et al. Characterization of apoptotic phenomena induced by treatment with L-asparaginase in NIH3T3 cells. Exp Cell Res. 1995;220(2):283-291.
16. Stams WA, den Boer ML, Beverloo HB, et al. Sensitivity to L-asparaginase is not associated with expression levels of asparagine synthetase in t(12;21)+ pediatric ALL. Blood. 2003;101(7):2743-2747.
17. Panosyan EH, Grigoryan RS, Avramis IA, et al. Deamination of glutamine is a prerequisite for optimal asparagine deamination by asparaginases in vivo (CCG-1961). Anticancer Res. 2004;24(2c):1121-1125.
18. Chan WK, Lorenzi PL, Anishkin A, et al. The glutaminase activity of L-asparaginase is not required for anticancer activity against ASNS-negative cells. Blood. 2014;123(23):3596-3606.
19. Narta UK, Kanwar SS, Azmi W. Pharmacological and clinical evaluation of L-asparaginase in the treatment of leukemia. Crit Rev Oncol Hematol. 2007;61(3):208-221.
20. Tong WH, Pieters R, de Groot-Kruseman HA, et al. The toxicity of very prolonged courses of PEGasparaginase or Erwinia asparaginase in relation to asparaginase activity, with a special focus on dyslipidemia. Haematologica. 2014;99(11):1716-1721.
21. Tong WH, Pieters R, Kaspers GJ, et al. A prospective study on drug monitoring of PEGasparaginase and Erwinia asparaginase and asparaginase antibodies in pediatric acute lymphoblastic leukemia. Blood. 2014;123(13):2026-2033.
22. Asselin BL, Whitin JC, Coppola DJ, Rupp IP, Sallan SE, Cohen HJ. Comparative pharmacokinetic studies of three asparaginase preparations. J Clin Oncol. 1993;11(9):1780-1786.
23. Ortega JA, Nesbit ME Jr, Donaldson MH, et al. L-Asparaginase, vincristine, and prednisone for induction of first remission in acute lymphocytic leukemia. Cancer Res. 1977;37(2):535-540.
24. Ho DH, Brown NS, Yen A, et al. Clinical pharmacology of polyethylene glycol-L-asparaginase. Drug Metab Dispos. 1986;14(3):349-352.
25. Keating MJ, Holmes R, Lerner S, Ho DH. L-asparaginase and PEG asparaginase--past, present, and future. Leuk Lymphoma. 1993;10 Suppl:153-157.
26. Ettinger LJ, Kurtzberg J, Voûte PA, Jürgens H, Halpern SL. An open-label, multicenter study of polyethylene glycol-L-asparaginase for the treatment of acute lymphoblastic leukemia. Cancer. 1995;75(5):1176-1181.
27. Dinndorf PA, Gootenberg J, Cohen MH, Keegan P, Pazdur R. FDA drug approval summary: pegaspargase (oncaspar) for the first-line treatment of children with acute lymphoblastic leukemia (ALL). Oncologist. 2007;12(8):991-998.
28. Avramis VI, Sencer S, Periclou AP, et al. A randomized comparison of native Escherichia coli asparaginase and polyethylene glycol conjugated asparaginase for treatment of children with newly diagnosed standard-risk acute lymphoblastic leukemia: a Children's Cancer Group study. Blood. 2002;99(6):1986-1994.
29. Pieters R, Appel I, Kuehnel HJ, et al. Pharmacokinetics, pharmacodynamics, efficacy, and safety of a new recombinant asparaginase preparation in children with previously untreated acute lymphoblastic leukemia: a randomized phase 2 clinical trial. Blood. 2008;112(13):4832-4838.
30. Li RJ, Jin R, Liu C, et al. FDA Approval Summary: calaspargase Pegol-mknl for treatment of acute lymphoblastic leukemia in children and young adults. Clin Cancer Res. 2020;26(2):328-331.
31. Maese L, Loh ML, Choi MR, et al. Recombinant Erwinia asparaginase (JZP458) in acute lymphoblastic leukemia: results from the phase 2/3 AALL1931 study. Blood. 2023;141(7):704-712.
32. Brigitha LJ, Pieters R, van der Sluis IM. How much asparaginase is needed for optimal outcome in childhood acute lymphoblastic leukaemia? A systematic review. Eur J Cancer. 2021;157:238-249.
33. Woo MH, Hak LJ, Storm MC, et al. Anti-asparaginase antibodies following E. coli asparaginase therapy in pediatric acute lymphoblastic leukemia. Leukemia. 1998;12(10):1527-1533.
34. Woo MH, Hak LJ, Storm MC, et al. Hypersensitivity or development of antibodies to asparaginase does not impact treatment outcome of childhood acute lymphoblastic leukemia. J Clin Oncol. 2000;18(7):1525-1532.

35. Panosyan EH, Seibel NL, Martin-Aragon S, et al. Asparaginase antibody and asparaginase activity in children with higher-risk acute lymphoblastic leukemia: Children's Cancer Group Study CCG-1961. J Pediatr Hematol Oncol. 2004;26(4):217-226.
36. Silverman LB, Gelber RD, Dalton VK, et al. Improved outcome for children with acute lymphoblastic leukemia: results of Dana-Farber Consortium Protocol 91-01. Blood. 2001;97(5):1211-1218.
37. Appel IM, Kazemier KM, Boos J, et al. Pharmacokinetic, pharmacodynamic and intracellular effects of PEG-asparaginase in newly diagnosed childhood acute lymphoblastic leukemia: results from a single agent window study. Leukemia. 2008;22(9):1665-1679.
38. Möricke A, Rizzari C, Alten J, et al. Hypersensitivity reactions to native E. coli L-asparaginase in children with acute lymphoblastic leukemia treated in Trial ALL-BFM 2000: impact of treatment schedule and type of glucocorticoid in induction. Hemasphere. 2023;7(6):e888.
39. Rizzari C, Möricke A, Valsecchi MG, et al. Incidence and characteristics of hypersensitivity reactions to PEG-asparaginase observed in 6136 children with acute lymphoblastic leukemia enrolled in the AIEOP-BFM ALL 2009 Study Protocol. Hemasphere. 2023;7(6):e893.
40. Eden OB, Shaw MP, Lilleyman JS, Richards S. Non-randomised study comparing toxicity of Escherichia coli and Erwinia asparaginase in children with leukaemia. Med Pediatr Oncol. 1990;18(6):497-502.
41. Albertsen BK, Schrøder H, Jakobsen P, Müller HJ, Carlsen NT, Schmiegelow K. Monitoring of Erwinia asparaginase therapy in childhood ALL in the Nordic countries. Br J Clin Pharmacol. 2001;52(4):433-437.
42. Albertsen BK, Schrøder H, Ingerslev J, et al. Comparison of intramuscular therapy with Erwinia asparaginase and asparaginase Medac: pharmacokinetics, pharmacodynamics, formation of antibodies and influence on the coagulation system. Br J Haematol. 2001;115(4):983-990.
43. Albertsen BK, Schrøder H, Jakobsen P, et al. Antibody formation during intravenous and intramuscular therapy with Erwinia asparaginase. Med Pediatr Oncol. 2002;38(5):310-316.
44. Rizzari C, Valsecchi MG, Aricò M, et al. Effect of protracted high-dose L-asparaginase given as a second exposure in a Berlin-Frankfurt-Münster-based treatment: results of the randomized 9102 intermediate-risk childhood acute lymphoblastic leukemia study--a report from the Associazione Italiana Ematologia Oncologia Pediatrica. J Clin Oncol. 2001;19(5):1297-1303.
45. Pession A, Valsecchi MG, Masera G, et al. Long-term results of a randomized trial on extended use of high dose L-asparaginase for standard risk childhood acute lymphoblastic leukemia. J Clin Oncol. 2005;23(28):7161-7167.
46. Duval M, Suciu S, Ferster A, et al. Comparison of Escherichia coli-asparaginase with Erwinia-asparaginase in the treatment of childhood lymphoid malignancies: results of a randomized European Organisation for Research and Treatment of Cancer-Children's Leukemia Group phase 3 trial. Blood. 2002;99(8):2734-2739.
47. Moghrabi A, Levy DE, Asselin B, et al. Results of the Dana-Farber Cancer Institute ALL Consortium Protocol 95-01 for children with acute lymphoblastic leukemia. Blood. 2007;109(3):896-904.
48. Kwok CS, Kham SK, Ariffin H, Lin HP, Quah TC, Yeoh AE. Minimal residual disease (MRD) measurement as a tool to compare the efficacy of chemotherapeutic drug regimens using Escherichia Coli-asparaginase or Erwinia-asparaginase in childhood acute lymphoblastic leukemia (ALL). Pediatr Blood Cancer. 2006;47(3):299-304.
49. Vrooman LM, Stevenson KE, Supko JG, et al. Postinduction dexamethasone and individualized dosing of Escherichia Coli L-asparaginase each improve outcome of children and adolescents with newly diagnosed acute lymphoblastic leukemia: results from a randomized study--Dana-Farber Cancer Institute ALL Consortium Protocol 00-01. J Clin Oncol. 2013;31(9):1202-1210.
50. Kloos RQH, Pieters R, Jumelet FMV, de Groot-Kruseman HA, van den Bos C, van der Sluis IM. Individualized asparaginase dosing in childhood acute lymphoblastic leukemia. J Clin Oncol. 2020;38(7):715-724.
51. Gupta S, Wang C, Raetz EA, et al. Impact of asparaginase discontinuation on outcome in childhood acute lymphoblastic leukemia: a report from the Children's Oncology Group. J Clin Oncol. 2020;38(17):1897-1905.
52. Maese L, Rizzari C, Coleman R, Power A, van der Sluis I, Rau RE. Can recombinant technology address asparaginase Erwinia chrysanthemi shortages? Pediatr Blood Cancer. 2021;68(10):e29169.
53. Van Trimpont M, Schalk AM, De Visser Y, et al. In vivo stabilization of a less toxic asparaginase variant leads to a durable antitumor response in acute leukemia. Haematologica. 2023;108(2):409-419.
54. Lin T, Hernandez-Illas M, Rey A, et al. A randomized phase I study to evaluate the safety, tolerability, and pharmacokinetics of recombinant Erwinia Asparaginase (JZP-458) in healthy adult volunteers. Clin Transl Sci. 2021;14(3):870-879.
55. Gao C, Ma X, Zhang Z, et al. Asparaginase Erwinia chrysanthemi for acute lymphoblastic leukemia and lymphoblastic lymphoma. Drugs Today (Barc). 2022;58(6):261-271.
56. Place AE, Stevenson KE, Vrooman LM, et al. Intravenous pegylated asparaginase versus intramuscular native Escherichia coli L-asparaginase in newly diagnosed childhood acute lymphoblastic leukaemia (DFCI 05-001): a randomised, open-label phase 3 trial. Lancet Oncol. 2015;16(16):1677-1690.
57. Salzer WL, Asselin B, Supko JG, et al. Erwinia asparaginase achieves therapeutic activity after pegaspargase allergy: a report from the Children's Oncology Group. Blood. 2013;122(4):507-514.
58. Rizzari C, Zucchetti M, Conter V, et al. L-asparagine depletion and L-asparaginase activity in children with acute lymphoblastic leukemia receiving i.m. or i.v. Erwinia C. or E. coli L-asparaginase as first exposure. Ann Oncol. 2000;11(2):189-193.
59. Tong WH, van der Sluis IM, Alleman CJ, et al. Cost-analysis of treatment of childhood acute lymphoblastic leukemia with asparaginase preparations: the impact of expensive chemotherapy. Haematologica. 2013;98(5):753-759.
60. Lin T, Dumas T, Kaullen J, et al. Population pharmacokinetic model development and simulation for recombinant Erwinia asparaginase produced in Pseudomonas fluorescens (JZP-458). Clin Pharmacol Drug Dev. 2021;10(12):1503-1513.
61. Inaba H, Pui CH. Advances in the diagnosis and treatment of pediatric acute lymphoblastic leukemia. J Clin Med. 2021;10(9):1926.
62. Maese L, Rau RE. Current use of asparaginase in acute lymphoblastic leukemia/lymphoblastic lymphoma. Front Pediatr. 2022;10:902117.
63. Vrooman LM, Supko JG, Neuberg DS, et al. Erwinia asparaginase after allergy to E. coli asparaginase in children with acute lymphoblastic leukemia. Pediatr Blood Cancer. 2010;54(2):199-205.