RESEARCH ARTICLE

Application of Mathematical Logic for Cytogenetic Definition and Risk Stratification of B-Cell Precursor Acute Lymphoblastic Leukemia (BCP-ALL)

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Abstract

BCP ALL is the most common phenotype of ALL. Identification of recurrent genetic abnormalities specific for BCP-ALL [i.e., t(12;21), t(17;19), t(1;19)], has become an essential tool for confirmation of diagnosis and risk stratification. It can also be used for assessing response to treatment and for detecting the re-emergence of malignant cells. Although the definition of BCP ALL with recurrent genetic abnormalities can be correctly expressed in verbal terms, Mathematical Logic may provide a definition that is more concise. We defined the semantics of conjunctions by the truth values "1" or "0". In a simplified syntax of English, the conjunctions "and", "or", "if and only if" were replaced by the symbols "∧ ", "V", "↔" respectively. This method permitted definitions stripped from all ambiguous elements.

Introduction

The role of Mathematical Logic in Medicine has been described previously (Zugmaier and Locatellli 2020). Although Mathematical Logic has been used for diagnosis and definition of disease (Bieganski 1909, Bochenski 1962, Gross 1969, Gross and Löffler 1997, Manzer 1925, Lin et al. 2014), its potential has not yet been fully explored (Gross and Löffler 1997).

In this study, we set out to describe Cytogenetic Definition and Risk Stratification of B-Cell Precursor Acute Lymphoblastic Leukemia (BCP-ALL) by Mathematical Logic.

Methods

The development of Mathematical Logic was described elsewhere (Zugmaier and Locatelli 2020). In brief, Mathematical Logic as used in this study was developed among others by the mathematicians Gottlob Frege (Thiel 1967) and Giuseppe Peano (Peano 1889), and the philosophers Bertrand Russell (Slater 1997) and Ludwig Wittgenstein (Wittgenstein 1992). Wittgenstein and the mathematician Emil Post (Post 1921) established the semantics of Mathematical Logic by truth tables, which are the basis of this study. True propositions are coded by the number 1, false propositions by the number 0. A proposition can only have one value at a time, 1 for "true" and 0 for "false". The values of 2 propositions can be listed by 4 permutations.

A	B
1	**1**
1	**0**
0	**1**
0	**0**

There are 2e4 = 16 permutations possible for truth values of a composite proposition "AB" consisting of 2 single propositions, "A ", and "B". Through this approach, the truth values of all propositions can be coded by a sequence of the numbers 1 and 0 (Zugmaier and Locatelli 2020). From the 16 possible logical connectives of 2 propositions, the ones used in this study are listed below.

Proposition I

A	B	AB
1	**1**	**1**
1	**0**	**0**
0	**1**	**0**
0	**0**	**0**

Verbal expression: Both A and B

Symbolic expression: A ∧ B

Proposition II

A	B	AB
1	1	1
1	0	1
0	1	1
0	0	0

Verbal expression: At least one A or B

Symbolic expression: A V B

Proposition III

A	B	AB
1	1	1
1	0	0
0	1	0
0	0	1

Verbal expression: If and only if A then B and vice versa

Symbolic expression: A ↔ B

Results

ALL has been described in detail elsewhere (Zugmaier and Locatelli 2020). In brief, it is defined by the presence of malignant lymphoblasts in the bone marrow and sometimes in peripheral blood. It is a systemic disease, which can involve any organ. Without treatment ALL is fatal. ALL is diagnosed in all ages, but it is the most common cancer of childhood (Zugmaier and Locatelli 2020). The chance of cure of patients with ALL has vastly increased because of risk stratification, more sophisticated diagnostic technology and optimization of chemotherapy (Moericke et al, 2008). Immune phenotyping by determination of clustered designation (CD) antigen has become the standard method to diagnose and classify leukemia. (Zugmaier 2019). BCP ALL is the most common phenotype of ALL (Borowitz et al. 2017) Identification of recurrent genetic abnormalities specific for BCP-ALL [i.e., t(12;21), t(17;19), t(1;19)], has become an essential tool for confirmation of diagnosis and risk stratification (Zugmaier an Locatelli 2020). Moreover, it can be useful also in assessing the response to treatment and for detecting the re-emergence of malignant cells after they have become undetectable after cytotoxic therapy. The most recent update of the classification of BCP-ALL was included in the latest edition of the World Health Organization (WHO) Classification of Tumors of Haematopoietic and Lymphoid tissues (Borowitz et al. 2017). A detailed overview on recurrent genetic abnormalities in ALL was published few years ago by Iacobucci and Mulligan (2017).

Although recurrent genetic abnormalities of BCP ALL can be correctly expressed in verbal terms, Mathematical Logic may

present the definition in a more concise way. We will use the semantics defined in the truth value tables described above and a simplified syntax of English. In the formulas, brackets "()" take precedence over each symbol, "∧" takes precedence over "V", the latter takes precedence over each one of "→ "and "↔" (Takeuti 1987).

BCP ALL with Recurrent Genetic Abnormalities is defined by the formula below.

BCP ALL with Recurrent Genetic Abnormalities ↔ t (9;22) (q34;p11.2) **V** (KMT2A(MLLL) rearrangement **V** t (12;21) (q13.2; q22.1) **V** ((hyperdiploid **V** hypodiploid) **∧** CD19 – positive **∧** CD10 – positive) **V** t (5;14) (q31.1; q32.1) **V** t(1;19)) (q23;p13.3) **V** t (17;19) (q23;p13.3) **V** Ph-like V iAMP21

This formula is stripped from all ambiguous elements (Halbach 2010).

For BCP-ALL, not only an exact diagnosis is essential but also the exact definition of risk factors of relapse (Hoelzer et al 2016). One of the most important risk factors is Minimal Residual Disease (MRD). The concept of treatment at the stage of MRD has resulted in better outcome and less side effects of treatment. A better term for MRD would be Measurable Residual Disease, because the disease is not minima, but the technology to measure disease burden has become more advanced (Locatelli et al. 2012).

The patient's clinical performance status is another important factor determining the risk of relapse since it influences the possibility of delivering intensive therapies. The 1st performance scale was developed by Karnofsky (Karnofsky and Burchenal 1949). Another one was developed by the Eastern Cooperative Oncology Group (ECOG) (Oken at al. 1982).

Karnofsky Status	Karnofsky Grade	ECOG Grade	ECOG Status
Normal, no complaints	100	0	Fully active, able to carry on all pre-disease performance without restriction
Able to carry on normal activities. Minor signs or symptoms of disease	90	0	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
Normal activity with effort	80	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
Care for self. Unable to carry on normal activity or to do active work	70	1	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
Requires occasional assistance, but able to care for most of his needs	60	2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours

Requires considerable assistance and frequent medical care	50	2	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
Disabled. Requires special care and assistance	40	3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
Severly disabled. Hospitalisation indicated though death nonimminent	30	3	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
Very sick. Hospitalisation necessary. Active supportive treatment necessary	20	4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
Moribund	10	4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
Dead	0	5	Dead

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Recurrent genetic abnormalities can be either favorable or unfavorable risk factors, depending on the type of abnormality detected in the leukemia cells (Iacobucci and Mulligan 2017, Sewdlow at al. 2017).

Increased risk of relapse $\leftrightarrow$ hypodiploid **V** t(17;19) **V** t (9;22) V KMT2A(MLL) **V** iAMP21 **V** Age $\geq$ 55 **V** ECOG > 1 **V** Leukocytes > 30 x 10e9 **V** Blasts day 15 > 5% **V** time to CR > 1 cycle **V** MRD – positive end of induction .

An increased risk of relapse can only be overcome aggressive treatment regimens such as allogeneic hematopoietic stem cell transplantation., For some risk factors such as Age $\geq$ 55 or ECOG > 1 or both, aggressive treatment is not possible.

Decreased risk of relapse $\leftrightarrow$ (hyperdiploid **V** t (12;21) **V** t (1;19)) **V** Age < 55 **∧** Leukocytes $\leq$ 30 x 10e9) **∧** ECOG < 2 **∧** Blasts day $\leq$ 15 < 5% **∧** MRD negativity end of induction

A decreased risk of relapse opens the perspective of cure in the absence of complications.

The semantic definition of truth values, with "true" being coded by 1 and "false" being coded by 0 avoids misunderstandings in the use of grammatical conjunctions. It is entirely possible to express these sematic definitions by the use of common English. The use of symbols just provides a more concise notation.

Discussion

In this study, we have described Mathematical Logic as a tool for definition of

disease and risk factors through the example for BCP ALL with recurrent genetic abnormalities. As method, we have used truth tables as developed by Wittgenstein (1992) and Post (1921). The truth value 1 was used for "true" and the truth value 0 for "false". This way the truth values of composite propositions could be determined by the truth values of single propositions and vice versa. Conjunctions such as "and", "or", "if and only if", defined by permutations of the truth values, were replaced by symbols as described above in detail. The importance of logic for diagnosis and definition of disease has been emphasized in various publications. Jevon's "Foundation of Logic" was called the "best a textbook of Medicine" (Cohen 1943, Gross and Löffler 1997). It has been stressed that no diagnosis is possible without logic (Cohen 1943, Gross and Löffler 1997, Biegansky 1909, Mainzer 1925, Gross 1968, Gross and Löffler 1997). However, a logical framework of medicine will never be complete because of the amount of permutations and the ever-changing concepts of disease (Gross and Löffler 1997). Therefore, the logical framework developed here does not have the ambition to describe the nature of disease or pathophysiologic mechanisms. It has the purpose to provide clear and concise definitions of diseases based on current knowledge. Formalized methods are not developed to replace the physician, but to provide the physician with a tool to improve diagnosis by methods that are more precise. In addition, the busy clinician may find it helpful to use Mathematical Logic as quick guidance for finding the correct diagnosis. By using Mathematical Logic to obtain definitions of diseases, stripped of all ambiguous elements (Halbach 2020), students have tools available, additional to textbooks, which can help them preparing for exams. However, in the end, physicians will always have the obligation to assess logical models in the context of clinical reality.

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