LEUKEMIC PROGRESSION AS PROCESS OF ADAPTATION (THEORETICAL MODEL)

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On the basis of an assumption that leukemic progression is a process of adaptation of normal hemopoiesis to the effect of the leukemic clone, a theoretical model of leukemia development is built.

General conclusions are as follows: the possibility of reaching remission depends upon suppression of normal hemopoiesis by cytostatics in a system of two cell populations: the duration of remission depends upon suppression of the leukemic clone; the quantity of blast cells of marrow in remission can exceed 5 per cent.

Key Words: Adaptation, Leukemia, Cell population, Internal energy, Spontaneous remission.

INTRODUCTION

Although considerable success in the treatment of leukemia has been made during the last decades, the essence of leukemia as a biological phenomenon seems unclear.

Further success in the understanding and treatment of leukemia is often associated with increasing interaction between biologists and clinicians.

One of the most promising directions in this interaction is to apply ideas on the process of adaptation in order to explain leukemic regularities of development and the phenomenon of spontaneous remission.

Data from the literature show that spontaneous remission of acute leukemia is associated with bacterial infection and is of short duration. It was also found that spontaneous remission is preceded by marked leucopenia and marrow hypoplasia. Leucopenia and suppression of normal hemopoiesis play an important role in the course of leukemia.

Leucopenia per se might be the most significant action of chemotherapeutic agents, rather than the direct tumor cell kill.

All data mentioned above fit well with the present theoretical model of leukemia development.

HYPOTHESIS

When starting to study any natural phenomenon one must be convinced that it can be subject to analysis, i.e. there are some general regularities of various forms of this phenomenon, independent of any random factors. In the case of leukemic progression this conviction is based on the fact that all leukemias proceed in stages. This peculiarity of all forms of leukemias does not depend upon either morphology of leukemic cells, their antigen characteristics or the type of chromosomal mutations in them.

It is suggested that we consider leukemic progression as a process of adaptation of normal hemopoiesis (NH) to the effect of the leukemic clone (LC). In other words, the change of stages of leukemia is a result of the interaction of normal tissue (NH) and the pathological one (LC). Therefore, NH and LC – two functional units, which determine the behaviour of each other – constitute one system.

Each stage of the leukemic process can be characterised by domination of NH or LC. Domination of NH will clinically correspond to remission of leukemia; LC in remission will be suppressed. Domination of LC will fit the first attack or a relapse of the disease; while NH will be in a subordinate (suppressed) state.

Two conclusions can be derived on the basis of the stages of development of leukemia:

1) The phenomenon of domination or subordination is not ‘innate’ for a certain cell population.
2) Every moment cell populations are in the state of a strict hierarchy of relations.

These existing hierarchical relations in cell populations lead us to the introduction of the conditional term ‘phase’ which determines the state of each cell population as compared with another population of the system at a given moment.

It should be kept in mind that there are only two possible states for cell populations at a given moment –
domination or subordination, while the number of phases equals the number of cell populations within the system. Besides, a cell population which stays in phase 'n' is to dominate over the cell population which stays in phase 'n+k' and is to be subordinate to the cell population in a phase 'n-k' provided these phases exist ('n' and 'k' are positive whole numbers).

Several cell populations cannot be in one and the same phase. If it were not so, hierarchy of cell populations would not have existed and leukemia would not have developed by stages.

Existence of stages in leukemic development allows us to introduce a new term: 'phase transition'. Phase transition is a change of states of cell populations, i.e. change of state of domination to state of subordination or vice versa for the two given cell populations.

Now the questions arise how is phase transition caused and what is the mechanism of realisation.

The above mentioned idea specifies leukemic progression as a process of adaptation of NH to effect of LC, therefore only NH can induce phase transition. Phase transition happens as soon as the system 'meets the row of critical states' and consists of a jump into a stable state.²

What is to be considered as the row of critical states?

The state of a system is uniquely defined by its internal energy (U), which is the sum of all sorts of energies present, such as mechanical energy, heat or chemical energy.¹³,¹²

The internal energy (U) of a system changes proportionally to the quantity of its elements.¹³,¹⁴

So, for a cell population the internal energy (U) depends mainly upon the quantity of its cells and the intensity of biochemical reactions in them (neglecting other less important parameters: volume, temperature, etc.).

The intensity of biochemical reactions is connected with states of a cell.

It is known that any cell can exist in one of the two states: stationary (G o) and active (G1,S,G2 and mitosis). The activity of some biochemical reactions in cells is minimal during the stationary period and increases during the active period. Suppression by antitumor drugs or by a certain cell population is expressed in the form of inhibition of biochemical reactions in the cells of this population and in the death of its cells.

It is clear that U of a cell population cannot be lower than a certain determined level (U-1). Let us assume that this corresponds to U of the population in the stationary state (G o). It is also obvious that U of a cell population cannot exceed a certain determined level (U-2) which theoretically corresponds to U of all cells in the active state. Existence of a cell population is possible only in the interval U-1–U-2. It is worth mentioning that in reality levels U-1 and U-2 can differ from the above mentioned, but they can serve as characterisation of this population. It is obvious that levels U-1 and U-2 will be 'flexible' for any cell population.

Phase transition may happen when U of a cell population approaches U-1 or U-2 levels. This process is to be accompanied by redistribution of energy in such a way that the stable existence of the system in new conditions is secured which permits to solve the problem of adaptation.²

Before we start to analyse practical options of leukemic development it is reasonable to make a theoretical summary hereof:

1) Normal hemopoiesis and a leukemic clone constitute one system.
2) Every cell population can be in one of the two states as compared to another: dominating or subordinate (suppressed).
3) The state of domination or subordination is determined by the phase (n, n+k or n-k) in which a certain cell population is found at the given moment.
4) Simultaneous existence of a number of cell populations in one and the same phase is excluded.
5) Every cell population is characterised by a certain level of internal energy, which is proportional to the quantity of cells and activity of their biochemical reactions.
6) The internal energy of a cell population can be neither lower nor higher than certain limits, which determine the borders of existence of this population.
7) Normal hemopoiesis is assumed to be able to induce a change of states of cell populations, i.e. phase transition. The leukemic clone is deprived of this capability.
8) Phase transition takes place when the internal energy of normal hemopoiesis approaches the critical level.
9) Phase transition from the dominating to the subordinate phase is accompanied by increasing internal energy of a cell population which accomplished this transition.
10) Phase transition from the subordinate to the dominating phase is accompanied by decreasing internal energy of a cell population which accomplished this transition.

Now let us consider the development of leukemia from this point of view.

There are three options regarding the comparative ability of one cell population to dominate over another:

1) LC > NH.
2) LC = NH.
3) LC < NH.

Let us analyse each of them.