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Transplants for acute myeloid leukaemia in 1st remission: standard of care or something else?

Keywords

Acute myeloid leukemia, clinical outcomes, prognosis, statistics.

Dear Editor,

In the previous issue of Cellular Therapy and Transplantation, Robert P. Gale published "Transplants for acute myeloid leukaemia in 1st remission: statisticians, magicians and the rest of us"[1]. The article delivers several messages:

1) Statistics is a lie that comforts people who do not have deep knowledge of the subject;

2) It is uncertain that we can predict relapse with reasonable accuracy;

3) It is unclear that hematopoietic stem cell transplantation (HSCT) can overcome the adverse biological features;

4) It is unclear that it is better to do the HSCT in the first complete remission (CR) that after relapse;

5) Transplant may kill the person who did not need it.

All of these statements might be very arguable thus, I believe that the Journal should publish an alternative point of view.

First. Recently the trend in science is to fight statistics and its predictive value and the theories of uncertainty. The greatest development they achieve in economics, lead by Nassim Taleb and his fellow swans (Fig. 1). The theory of Nassim Taleb is based on several points: the black swans were the synonym for something non-existent in England until Australia was discovered where black swans do actually exist; human societies develop explosively based on rare events, the "black swans"; economics is the most volatile part of development in societies; statistics and predictions work until some rare unique event (Fig. 1A); as soon as one unpredictable event happened the other "black swans" tend to come over (Fig. 1B); since we are not capable of predicting unknown, the statistics and prognosis are a certain form of placebo for disasters [2].

One of his examples is about the turkey which is fed every day by friendly members of the human race looking out for its best interests. If it applied statistics it would prove this notion with high significance…until the Easter comes.

However, what is applied to economics could hardly be applied to biological systems, as they are based on conservative biological mechanisms and systems of regulation.

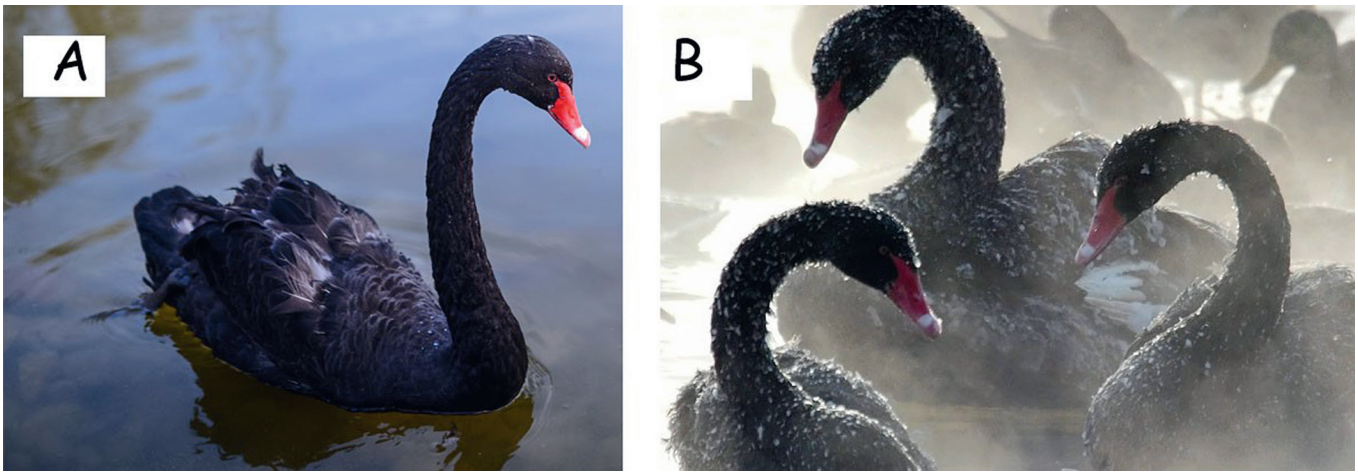

Figure 1. Black swans tend to group together. (A) Single black swan. (B) Many black swans together

The fact that human genome is a subject to substantial variability and we still do not know the interactions within it [3] does not mean that the events happening are random. And if one "black swan", like acute myeloblastic leukemia came, does not mean that the rest of the events are random and we cannot predict anything with greater certainty than 50:50.

Second. We cannot predict a relapse with reasonable accuracy in a single patient, however, we can do that in one thousand patients, and with less accuracy in one hundred patients, and even with less accuracy in ten patients. The claim that individualized therapy is the "state of art" and there are "great artists" and "not so great" is a subject of a great speculation in alternative medicine in oncology. However, the comparative trials demonstrate shorter survival in alternative medicine users [4]. The question of rejecting population-wide treatment decisions is rather a question of psychological issues of dealing with not perfect expected treatment results [5]. This is hard both on the physician's side and on the patient side. However, getting 50/50 results with flipping a coin is not better than being intentionally wrong 1/3 of the times with current state of diagnostics and treatment.

Third. Indeed it is unclear that HSCT can overcome adverse biological features, but this is also true for the other current treatment options in AML. Particularly discouraging are the results of the German-Austrian AML Study group regarding p53-mutated AML with complex karyotype. These patients even after one of the most aggressive chemotherapy that is used by the Group and HSCT in the 1st CR have 0% probability of long-term survival [6]. Should we subject these patients to palliative care at diagnosis? Or should we conduct a randomized trial of palliative care versus intensive chemotherapy and HSCT in the 1st CR with pharmacoeconomic analysis and QALY estimation? Most of the physicians will give the most effective treatment at that time, though the evidence might be not there.

Fourth. Although there are several randomized trials comparing HSCT in the first CR versus observation [7, 8]. These trials were conducted in the 1990s and demonstrated moderate or no improvement in overall survival. This was due to non-relapse mortality, and mostly in the unrelated donor setting where it reached 20%. Nonetheless, all the recent studies demonstrate non-relapse mortality of about 5-10% even after unrelated and haploidentical grafts [9, 10]. Thus, if these randomized trials would have been conducted nowadays the improvement in the transplant arm was expected to be 5-15% with a significant difference. Also there are different target strategies, like sorafenib that fail in the chemotherapy setting [11], but demonstrate very low relapse incidence after allogeneic HSCT [12].

Fifth. Indeed, the currently existing treatments in AML do kill people. How unfortunate were M3 AML patients who just five years ago received TAD-HAM induction and died. They should have received arsenic trioxide with retinoic acid [13]. Unfortunately, this is a common situation in medicine. Louis Goodman could not have known that Hodgkin's disease would be one of the most curable hematological malignancies [14]. Although the progress in AML was disappointing [15], this is not the motive to discourage the use of most effective treatments like HSCT in the 1st CR.

The current recommendations of EBMT [16] state that HSCT in the first CR is the standard option except t(16:16) and t(15:17) part of t(8;21) variants and this represents the existing evidence. Unfortunately, despite all discussed drawbacks of this method, no better options exist.

To conclude, indeed there is an existing risk to harm a patient with the decision to perform HSCT in the first CR. It is hard to argue with Robert Gale [1] that there are no instruments for individual prognosis in AML, but instead of admitting uncertainty the population-wide medical decisions should be made. Also HSCT is a rapidly improving discipline of medicine that can change even the currently existing indications for HSCT.

Ivan S.Moiseev

PhD, R. Gorbacheva Memorial Institute of Children Oncology, Hematology and Transplantology, The St. Petersburg State I. Pavlov Medical University, St. Petersburg, Russia

E-mail: moisiv@mail.ru

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Reply by Prof. Robert P. Gale

I thank Prof. Moiseev for his thoughtful letter. The notion of the black swan, albeit in a slightly different context, was 1st proposed by Aldous Huxley who noted if your hypothesis is all swans in the world are white you should not look to prove yourself by looking for white swans (you would need to see every swan in the world) but rather look for a black swan. If you see one you know your hypothesis is wrong. The message is good scientists try to disprove rather than prove their hypotheses. Sadly, this is rare; most people try to prove themselves right, not wrong. The result in many errors. About one-half of our medical practices are either wrong or harmful. Medical reversals are common. Consider autotransplants for breast cancer and reduced-intensity transplants to decrease transplant-related mortality as relevant examples. I could add radical mastectomy for breast cancer, percutaneous stents for angina pectoris and many more.

My point regarding transplant in acute myeloid leukaemia in 1st remission is simple. Randomized clinical trials provide answers for cohorts. However physicians make recommendations to a person, not to a cohort. Consequently, what we need to know is the concordance statistic (C-statistic) from a receiver-operator characteristic (ROC) curve for predictive variable(s) for relapse in a person with AML in 1st remission on which we make a recommendation for a transplant or not. Analyses of prediction accuracy in a person with AML in 1st remission using cytogenetics, the European LeukemiaNet risk classification, results of measurable residual disease (MRD)-testing and other predictive variables alone or combined have C-statistics of 0.70-0.08. This means a physician with be wrong predicting relapse in about 1 to every 3 or 4 persons he sees. The contrary is also so, predicting no relapse will be wrong in 1 in every 3-4 persons. Is this OK? The bottom line is how willing a physician is to be wrong. And how willing is a patient to receive a prediction which is wrong. When the proposed intervention has little risk and substantial potential benefit these error rates are likely acceptable to both. However, this is not so for transplants where it is quite possible to kill someone already cured by chemotherapy.

As physicians we work with imperfect knowledge. Voltaire said: *Uncertainty is not a pleasant condition but certainty is an absurd one*. The important thing is to recognize this uncertainty and indicate the level of uncertainty to their patient. This allows the patient to make an informed decision. Statements such as: *You are going to relapse and **need** a transplant* are statistically and ethically wrong. Nobody likes to live with uncertainty but this is our fate as physicians because of substantial unexplained variance some of which might ultimately be sorted out by discovering presently unknown (latent) variables. However, we will never explain all variance because of 2 factors we cannot control: measurement error and chance. As Sir William Osler, the great British, Canadian and American physician noted: *Medicine is a science of uncertainty and an art of probability*. Learn to live with it. Perhaps we can slug this out when I visit his Institute in September. No black swans please!

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Robert Peter Gale
MD, PhD, DSc(hc), FACP, FRSM

Haematology Research Centre
Division of Experimental Medicine
Department of Medicine
Imperial College London, London, UK
E-mail: robertpetergale@alumni.ucla.edu

Трансплантация при остром миелобластном лейкозе в первой ремиссии: стандарт лечения или что-то другое?

Иван С. Моисеев

НИИ детской онкологии, гематологии и трансплантологии им. Р. Горбачевой, Первый Санкт-Петербургский государственный медицинский университет им. И. П. Павлова, Санкт-Петербург, Российская Федерация

Резюме

В предыдущем номере *Cellular Therapy and Transplantation* Robert P. Gale опубликовал статью «Трансплантация при остром миелобластном лейкозе в первой ремиссии: статистики, маги и мы, все остальные», где он пишет о ряде проблем при выборе дальнейшей тактики после индукции ремиссии лейкоза. Вкратце, основные тезисы статьи звучат следующим образом: статистика – это «ложь», успокаивающая людей без знания этого предмета; мы не можем предсказать рецидив после химиотерапии со значимой достоверностью; не доказано, что трансплантация позволяет преодолеть негативные биологические свойства опухоли; неизвестно, лучше ли делать трансплантацию в первой ремиссии, чем после рецидива, трансплантация может привести к летальному исходу от осложнений у пациентов, которые в ней не нуждаются. Хотя в последнее время в научной среде активно развеваются идеи низкой значимости статистики и моделирования, такие как, например, теория «черного лебедя» Нассима Талеба, существуют значительные отличия между общественными науками и медициной. В письме в редакцию обсуждаются текущие данные об эффективности трансплантации в первой ремиссии острого миелобластного лейкоза, необходимость популяционных медицинских рекомендаций и психологические аспекты применительно к врачу и пациенту, связанные с назначением такого несовершенного метода лечения, как трансплантация гемопоэтических стволовых клеток.

Ключевые слова

Острый миелобластный лейкоз, исходы, прогноз, статистика.