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How do haematopoietic cell transplants cure leukaemias?

¿Cómo curan los trasplantes las leucemias?

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Haematopoietic cell transplants are widely used to treat persons with leukaemia. Over one-half million have been done worldwide. Considerable data indicate these transplants have greater anti-leukemia efficacy than conventional therapies. Whether this results in better survival is controversial but this benefit is clearest in persons with leukaemia not achieving remission with current non-transplant therapies. The question arises: when successful, how do transplants cure leukaemia? This question is the subject of this commentary.

There are at least 5 ways by which hematopoietic cell transplants might appear to cure including: *1)* transplanting persons cured before the transplant; *2)* anti-leukaemia efficacy of high-dose therapy; *3)* immune-mediated anti-leukaemia effects; *4)* effect of stochastic considerations on relapse probability; and *5)* mistaking *operational cure* for true *cure*. Let's consider each mechanism.

A substantial proportion, perhaps one-third of persons receiving a haematopoietic cell transplant are cured pretransplant. Their post-transplant *freedom-from-relapse* is unrelated to their receiving a transplant. This situation arises because we are unable to accurately predict which persons achieving and remaining in complete remission for 3-6 months are likely to relapse. Tests such as cytogenetics, mutation analyses and measureable residual disease (MRD)-testing are inaccurate predictors in persons in remission at 3-6 months. For example, MRD-test results in person in complete remission after completing consolidation chemotherapy have about 30 percent false-negative and -positive results. The C-statistic (a measure of accuracy) derived from receiver operator characteristic (ROC) curves for MRD-test results in recent clinical trials is about 0.7 suggesting high level

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of mis-assignment of *cure*. The only situation where we can be reasonably certain transplants are being done in persons not already cured is in the setting of failure of conventional therapies. Here the cure rate is about 20 percent.

The early rationale for doing haematopoietic cell transplants was to allow giving high-dose therapy including drugs and radiation. We now know no dose of therapy we give completely destroys normal bone marrow function. However, infusing haematopoietic cells accelerates bone marrow recovery. We can estimate the impact of high-dose therapy be comparing leukaemia relapse rates in persons receiving high-dose *versus* reduced-intensity pretransplant therapy (RIC) after adjusting for variables associated with leukaemia relapse. In almost all settings persons receiving RIC transplants have a greater likelihood of relapse than persons receiving high-dose pretransplant therapy. The difference in relapse rates is 10-20 percent. These data indicate high-dose therapy is another way haematopoietic cell transplants cure leukaemia.

Considerable data suggest immune-mediated anti-leukaemia effects (sometimes referred to as graft-*versus*-leukaemia or G*v*L) operate after allotransplants. For example, relapse risk is increased in persons without acute or chronic graft-*versus*-host disease (G*v*HD), recipients of T-cell-depleted transplants and recipients of transplants from genetically-identical twins. In contrast, relapse risk is decreased in persons with acute and chronic G*v*HD (these are confounded). These data suggest an immune-mediated anti-leukemia effect after allotransplants. This anti-leukaemia effect is not proved leukaemia-specific and may simply be a result of G*v*HD directed at disparate histocompatibility antigens rather than leukaemia-specific antigen. Whether it operates in an autologous setting is unknown and unproved except in artificial setting such as genetically modified T-cells (such as chimeric antigen receptor ([CAR] T-cells).

We cure a substantial proportion of persons with leukaemia. However, it is unclear how this is achieved. It is unlikely we eradicate all leukaemia cells in a person with leukaemia. Considerable data from the A-bomb survivors and other settings indicate, fortunately, it is unnecessary to eradicate every leukaemia cell to cure leukaemia. For example, the interval from the time BCR/ABL is formed to develop radiation-induced chronic myeloid leukaemia (CML) in the A-bomb survivors can take 40 or more years. This means a person with a few residual leukaemias cells may die of a competing cause before one or more of these residual leukaemia cells undergo sufficient numbers of divisions to eventuate in clinical relapse. The process by which this occurs is termed stochastic.

These stochastic effect should be distinguished from a 5th mechanism, mis-identification of persons as *cured* when they are not. For example, most persons with leukaemia are old. Many destined to relapse may die of another event (cardiovascular disease, another neoplasm) before their leukaemia has sufficient time to relapse. The situation in these persons is best termed operational cure to distinguish it from real cure (This distinction is important to the biologist but not to the person with leukaemia).

The increased likelihood of cure in persons receiving an allotransplant is the sum of these mechanisms. The proportional contribution of each mechanism will likely differ in different leukaemias, different disease states and different persons including those with the same leukaemia and disease state. This makes quantification of the impact of these mechanisms in a person difficult or impossible. Other mechanisms may also operate. Regardless of the mix of different mechanisms in different persons with leukaemia the net result is a lower risk of leukaemia relapse after allotransplants. Whether this benefit results in a survival advantage is controversial.