Effects of hydroxyurea on T cell count changes during primary HIV infection

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Hydroxyurea affects the synthesis of deoxynucleoside triphosphates, by inhibiting the cellular enzyme ribonucleotide reductase [1]. By this mechanism hydroxyurea can prevent mitosis, therefore it is classified as a cytostatic drug [2]. Moreover, cellular deoxynucleoside triphosphate levels represent a limiting factor for the completion of retroviral reverse transcription [3,4]. On this basis, hydroxyurea was originally proposed as an anti-HIV drug [3]. Hydroxyurea inhibits HIV in active and resting CD4 T lymphocytes and macrophages, potentiates the activity of nucleoside reverse transcriptase inhibitors (NRTI), compensates for resistance to adenosine analogue NRTI, and increases the phosphorylation of pyrimidine NRTI (for a review, see Ref. 5). Data from randomized, controlled clinical trials involving more than 500 patients [6-9] indicate that hydroxyurea is safe and augments the suppression of HIV replication when used in combination with didanosine (ddI) or ddI/stavudine as initial therapy in patients without extensive antiretroviral experience.

T cell count recovery is a parameter used to evaluate the effectiveness of antiretroviral regimens. An increase in the CD4 cell count is viewed as a beneficial consequence of highly active antiretroviral therapies (HAART), and as an indicator of immune recovery. On the other hand, proliferating CD4 T lymphocytes are permissive to productive HIV replication. Mathematical models [10-14], based on a `prey-predator' equilibrium, predict that a sustained expansion of the CD4 T lymphocytes subset - the `prey' - increases the probability that HIV - the `predator' - spreads. This assumption was supported by a recent clinical study [15], showing a positive correlation between CD4 T lymphocyte increases and viral rebound in patients shifted from triple to bi- or monotherapy. As a corollary, the inclusion of cytostatic drugs in antiretroviral combinations may have a beneficial outcome.

Although hydroxyurea has cytostatic properties, the actual impact of these effects on the immune system is still poorly understood. Four randomized clinical trials [6-9] evaluated the effects of hydroxyurea-based antiretroviral regimens in HIV patients at various stages of infection, except during primary HIV infection (PHI). A blunt increase, or no increase of CD4 cell count was consistently observed in the hydroxyurea-containing arms. However, a significant increase in the CD4 cell count was reported after treatment of patients during PHI with hydroxyurea plus ddI plus indinavir [16]. It is not clear whether the CD4 cell count increase observed in the latter trial was due to a lack of cytostatic effects from hydroxyurea or simply to the fact that PHI is naturally characterized by an increase of CD4 cell count after the initial decline, even in the absence of therapy. This natural return of CD4 T lymphocytes might have `masked' the cytostatic effects of hydroxyurea.

In order to investigate the impact of hydroxyurea cytostatic effects during PHI, we evaluated the changes in peripheral T lymphocyte count in two HAART-treated PHI cohorts, one of which received hydroxyurea-containing combinations.

Nineteen patients were treated with a quadruple combination without hydroxyurea (zidovudine + lamivudine + ritonavir + saquinavir, defined as hydroxyurea-negative arm). This group was matched, on the basis of the diagnosis of PHI and on CD4 cell count before treatment (CD4 cell count ≥ 300/mm$^3$), with another group of patients (hydroxyurea-positive arm) treated with regimens including hydroxyurea (hydroxyurea + ddI + indinavir: eight patients; hydroxyurea + ddI + nelfinavir + nevirapine or delavirdine: two patients). Plasma viraemia, measured by branch-DNA, and the peripheral CD4 and CD8 cell counts were analysed at weeks 0, 2, 4, 8, 12, 24, 36 of therapy.

The antiretroviral potency of both regimens was comparable. In fact, the curves representing the decrease of plasma viraemia over time in the hydroxyurea-negative and hydroxyurea-positive arms were overlapping (Fig. 1a). The average decrease in plasma viraemia at the last time point (week 36) was of 2.86 log in hydroxyurea-negative and of 2.99 log in hydroxyurea-positive, respectively. The changes in the CD4 : CD8 cell ratio after therapy were also very similar (Fig. 1b). In both the hydroxyurea-negative and -positive arms, CD4 : CD8 cell ratios increased and tended to normalization (average at week 36, 1.1 and 1.04,
In contrast, the evolution of the CD4 and CD8 T lymphocyte populations during the after-treatment follow-up differed between the two cohorts. Consistent with the previous observation [16], the CD4 cell count increase was of +142 cells/mm$^3$ after 12 weeks in the hydroxyurea-positive arm. However, a gain of only +44 cells/mm$^3$ was observed in the hydroxyurea-positive arm after 36 weeks of follow-up (Fig. 1 c). In contrast, the CD4 cell count increase in the hydroxyurea-negative group was +242 cells/mm$^3$. The evolution of CD4 cell count in time was statistically different between the two groups, depending on the treatment [$F = 5.52; P = 0.026$, data analysed by repeated-measures multivariate analysis of variance]. Finally, we analysed the CD8 cell count during the 36 week follow-up. As shown in Fig. 1 d, although the average CD8 cell count was higher in the hydroxyurea-positive arm than in the hydroxyurea-negative arm at baseline, the CD8 cell count decline became more pronounced in the hydroxyurea-positive arm soon after starting the treatment. The CD8 cell count remained lower in the hydroxyurea-containing arm at all times after therapy. At week 36, the average CD8 cell count decrease in the hydroxyurea-containing arm was -789 cells/mm$^3$, whereas the decrease in the hydroxyurea-negative arm was only -336 cells/mm$^3$.

Our results are consistent with a cytostatic effect of hydroxyurea on T cells. By exerting its activity on both T cell subpopulations, hydroxyurea appears to limit the increase in the absolute number of CD4 T lymphocytes, while exacerbating the decrease of CD8 T lymphocytes. The result is an increase in the CD4 : CD8 cell ratio identical to that observed in the absence of hydroxyurea. This is consistent with the report that relative percentages, but not absolute numbers of CD4 T lymphocytes, increased after hydroxyurea-containing treatments [6]. The net changes in circulating T cell count are probably the composite of proliferation, redistribution between peripheral and lymph node compartments [17] and, mainly for the CD4 T lymphocytes, cell death, mediated by either HIV or immune cytopathic effects [18,19]. Although our data do not permit us to determine the absolute impact of each of these events, the modest CD4 cell count recovery in the presence of hydroxyurea, despite viremia reduction, is suggestive of a limited T cell proliferation, as it results from the simplified equation: `T cell count = T cells produced + T cells released from lymph nodes - CD4 cells destroyed'.
and positive arms, one can approximate that the amount of T lymphocytes destroyed is comparable in the two groups. Moreover, at present there is no evidence that the T cell redistribution from the lymph nodes, as a consequence of a reduced antigen-dependent inflammatory status, is affected by hydroxyurea. The resulting CD4 cell count is thus probably influenced by the proliferation rate. This conclusion is supported by the data describing CD8 T lymphocyte changes. The decline in the CD8 cell count in the presence of hydroxyurea, far exceeding that expected in response to decreased viraemia levels (as found in the hydroxyurea-negative group), also argues for a reduced basal proliferation rate.

At present, there is no indication that the limited expansion of the CD4 cell compartment, observed when hydroxyurea is used in the context of an effective antiretroviral therapy, might be detrimental to the reconstitution of the immune system. On the contrary, a growing number of reports [20-23], indicate that immunological parameters and functions improve under continued hydroxyurea-containing antiretroviral therapy. A net increase of naïve T lymphocytes has been consistently observed after hydroxyurea-based HAART was administered to patients with PHI as well as chronic HIV infection [21,22]. Control of infection upon the complete discontinuation of hydroxyurea-based regimens has also been described [20,23].

References


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