High-dose chemotherapy and autotransplants: A time for guidelines

In recent years we have witnessed an almost exponential increase in the use of high-dose chemotherapy followed by autologous cryopreserved hematopoietic cells. In fact, the more than 8000 autotransplants performed in Europe in 1995 [1] represent an almost four-fold increase over the number performed in 1990, and more than a 40-fold increase over the less than 200 autografts recorded each year in the early 80s [2].

The reasons for this dramatic rise are undoubtedly the ease with which we are now able to harvest very large amounts of circulating progenitor cells (CPC), and the speed with which the autografted patients recover normal granulocyte and platelet counts following myeloablative treatments (for a review, see To et al. [3]). In fact, the post-transplant aplastic phase, while still of a grade 4 in severity according to common toxicity criteria, has become so brief that myelotoxicity per se no longer limits the use of high-dose chemotherapy and radiotherapy. In essence, we are now able to design and test new therapeutic strategies thus far precluded by unacceptably protracted hematological toxicity. As a consequence, high-dose treatments can now not only be delivered early in the course of poor-prognosis tumors as part of their first-line therapeutic approach, but we can design multicyclic myeloablative regimens as well as non myeloablative multiple courses in trying to maximize cytotoxic dose intensity.

It is really impossible, as well as unwise, to predict the clinical results of this resetting at a higher level of the conventional dose limits established when drugs were given without CPC support, or to anticipate the therapeutic impact of the new treatment strategies (e.g., high-dose intensive therapy, high-dose sequential therapy, total therapy, rapidly cycled chemotherapy) [4-7] made possible by this approach. Far from having reached a concluding stage, we have just entered an exploratory phase whose main goal is to define the feasibility, tolerability and toxicity of chemotherapy given according to these new rules. And it is in this light that we should consider the two papers reported by Culine et al. and by Honkoop et al. in this issue of Annals of Oncology [8, 9].

Both groups employed CPC to deliver repeated cycles of non myeloablative, yet severely myelotoxic chemotherapy, planned for every three weeks for a total of three to four cycles. The paper by Honkoop et al. described a dose-finding study in which the amount of doxorubicin and cyclophosphamide were escalated in cohorts of three patients up to their maximum tolerable dosages (MTD). The MTD for the combination was defined as doxorubicin 110 mg/m²/wk, and cyclophosphamide 4000 mg/m²/wk, which represents approximately three-fold and five-fold increases, respectively, in the average dose intensity of the same combination when given in the absence of CPC reinfusion, with or without growth factor support. A different study design was adopted by Culine et al., who arbitrarily set the doses of the drugs chosen at an intermediate-high level, combined them in a sequential design alternating doxorubicin plus cyclophosphamide with etoposide plus carboplatin, and assessed the feasibility and safety of this intended program in chemotherapy-naive patients with metastatic cancer. Only three of 30 enrolled patients discontinued the treatment because of toxicity, and the authors conclude that support with CPC and growth factors allows the safe and timely administration of repetitive cycles of intermediate-high doses of chemotherapy.

A further notable difference between the two papers is the strategy adopted for CPC procurement. In fact, while Culine et al. exploited the mobilizing effect of the first chemotherapy cycle to facilitate CPC procurement, Honkoop et al. chose to rely only on growth factor mobilization. The comparison leaves no doubt about which should be considered the better strategy. Culine et al., using a standard dose of G-CSF (i.e., 5 μg/kg per day) were able to collect a median number of 10 × 10⁶ CD34+ cells per kg of body weight (range 8–30) through a single apheresis procedure (range 1–3). Conversely, Honkoop et al. treated a very similar chemotherapy-naive patient population with G-CSF at 15 μg/kg per day for approximately one week prior to the first chemotherapy cycle. They were able to harvest a median of 6 × 10⁶ CD34+ cells per kg (range 2–17), and a median of three leukaphereses were required (range 1–5). Interestingly, when the CD34+ cell yield was inadequate, the authors were able to harvest the required amount through one or two leukaphereses performed after the first cycle of chemotherapy. CPC mobilization with high-dose G-CSF alone is certainly the only strategy in normal CPC donors worth pursuing. In contrast, in cancer patients with a normal bone marrow reserve, it is hard to appreciate a procedure that uses a poorly tolerated and expensive course of high-dose G-CSF, delays the start of a chemotherapy treatment (which in any case is necessary), and requires multiple procedures to harvest, on the average, half the amount of CD34+ cells that can be easily collected through a single apheresis when standard-dose G-CSF is given after the first chemotherapy cycle.

While assessment of the anticancer activity of the treatments employed could not be a primary study objective, the authors appropriately also provided activity data, reaching opposite conclusions. According to Hon-
koope et al. the response data, when compared to the results of less intensive regimens using the same drug combination, do not encourage the use of their high-dose program in a randomized study in advanced breast cancer. Conversely, Culine et al. judged the over 75% response observed in small-cell lung cancer and poorly differentiated carcinoma of unknown primary site as sufficient motivation for a phase II trial. On the basis of these data on the whole, it would be equally unwise to condone or reject high-dose chemotherapy. As for any standard-dose combination, each high-dose regimen should be carefully tested and individually assessed for both toxicity and efficacy rather than judged collectively.

Whatever the final role for their high-dose approach, the two papers represent a strong argument in favor of the use of CPC also following non-myeloablative combinations. This has been clearly demonstrated only in the Honkoop et al. paper, since the MTD of the drug combination used without CPC support had already been defined by previous studies of the same group [10]. Nonetheless, there is little doubt that the four-step high-dose sequential chemotherapy program of Culine et al. would not be feasible without CPC support. This is not true, however, for all intermediate-dose regimens, and the need for CPC support should as far as possible be proven before incorporating this supportive measure in a treatment program. Fielding et al. [11], for example, have recently shown that the reinfusion of CPC following miniBEAM chemotherapy did not accelerate hematopoietic recovery. While this negative result may simply reflect the very low amount of CPC infused, their report underscores the need for an accurate assessment of the benefit of CPC use under the specific conditions chosen.

Finally, the emerging role of CPC reinfusion used solely as a supportive measure following non-myeloablative multiple courses raises critical economic issues. It is almost universally acknowledged that the use of CPC has rendered high-dose chemotherapy, even of the myeloablative type, a feasible and safe procedure in peripheral hospitals [12] and in the outpatient setting [13]. Nonetheless, the prodigious hospital and clinical costs for the procedure (typically US$80,000 to US$150,000, with wide inter-country fluctuations) have remained essentially the same as when the treatment required extended hospitalization, intensive nursing care, specialized inpatient facilities, and expensive supportive measures. The much reduced costs and unchanged high fees have brought extraordinary popularity to this form of treatment, regardless of proven clinical benefits. Many centers now consider high-dose chemotherapy an easy way to balance budgets. In this respect, multiple CPC transplantations, by multiplying three to four times the extraordinary revenues of these outpatient procedures, promise to represent a bonanza for the benefiting centers, as well as additional costs for national Health Services.

It has always been our strong conviction that high-dose therapy can not have a clinical impact unless it is widely available, and the use of CPC was explored from the beginning with this specific goal in mind [14]. Nonetheless, established indications are still few, and certainly they neither justify nor require the widespread application of this procedure. It is clearly time for the onco-hematologic community to set clear regulations not only for the collection and processing of CPC, but also for the use and refunding policy of CPC autotransplants. Minimal guidelines for progenitor cell processing and transplantation have already been developed by scientific societies representing both laboratory investigators (e.g., ISHAGE) and clinical transplant physicians (i.e., ASBMT and EBMT). Compliance with these minimum guidelines should soon be enforced through an accreditation/inspection program to protect patients who receive autotransplant, while rewarding the performing centers with an equitable payoff, and without inhibiting ongoing clinical research. Failure to do so might severely jeopardize the rapid and sustainable development of this potentially life-saving modality of therapy.

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References

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