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Glutamine parenteral supplementation in stem cell transplant

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Pytlik *et al*[1] recently described the results of a randomized double-blind placebo-controlled study on alanyl-glutamine dipeptide administered in autologous transplant patients. What is really surprising is not only the lack of any effect of glutamine supplementation but the detrimental effect, which was statistically significant, on several end points of the study (survival, hospitalization, mucositis, opioid requirements, and relapse). If our first goal is 'first do no harm', the results of this study obviously do not go in this direction and this raises the question of a premature withdrawal of the study, considering also the significant increment in the cost of the transplant procedure. Although several adjustments were made by the authors in dissecting the patient population, excluding multiple sclerosis and multiple myeloma, these were not responsible for major differences in their results. Heterogeneity of the patient population as stated by the authors might be responsible for the lack of any effect. We would like to draw attention to the following points with regard to patient characteristics and the design of the above-mentioned study:

1. disease status, which is highly relevant to the outcome of transplant, was not reported. The authors state that the transplant was performed as first-line treatment in the majority of patients in both groups, but no other specifications were given and this may account for the difference in the relapse rate and overall survival that was statistically significant;
2. with regard to the transplant procedure, we point out the low myeloablative potential of most of the conditioning regimens adopted and, consequently, the difficulty of detecting any difference between the groups;
3. glutamine was not given as a supplementation of total parenteral nutrition (TPN), but rather as an adjunctive treatment from days $+1$ to $+14$ after stem cell infusion or to discharge, independent of TPN administration. In fact, TPN mean duration was very short at 3.5 days in the glutamine group and 2.8 days in the placebo group, despite prolonged duration of severe mucositis requiring opioids;
4. the schedule of glutamine supplementation adopted in this study could cause an unbalanced amino-acid intake (according to the manufacturer's instructions, Dipeptiven should represent at the most 20% of total amino-acid intake), and this in turn could be responsible for the lack of benefits.

Dipeptiven- and glutamine-enriched parenteral formulas were studied in two consecutive randomized clinical trials at our institution in patients undergoing high-dose chemotherapy and autologous peripheral blood stem cell transplantation for hematological malignancies.[2] The Dipeptiven group received daily parenteral nutrition comprising Kabimix™ 1830 (Fresenius Kabi, Uppsala, Sweden), hydrosoluble and liposoluble vitamins and Dipeptiven™ (Fresenius Kabi, Uppsala, Sweden) 100 ml (glutamine 13.46 g according to the manufacturer's instructions), while the placebo group received daily parenteral nutrition comprising Kabimix™ 1830 and hydrosoluble and liposoluble vitamins from day $+1$ after a PBSCT until discharge. Lymphocyte count $>0.5 \times 10^9$/l was achieved on day 18 after stem cell infusion in patients receiving supplementation with glutamine and on day 29 in the placebo group, $P=0.009$. Lymphocyte subset analysis showed a significant increase in the CD8+ subset on days $+15$ and $+30$ and a normalization, on day $+60$, of the usual early post transplant overshoot of the CD16+CD56+ subset. Mucositis assessed by daily mucositis score by DMS[3,4] was unaffected by glutamine supplementation with Dipeptiven™. While we do confirm a substantial lack of effect on fever, mucositis, infections and length of hospitalization, we found that glutamine supplementation after autologous stem cell transplantation was safe and efficacious and improved lymphocyte recovery; further studies are needed to assess clinical benefits of such an approach to justify its economical impact.

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