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Feasibility of a dose-adjusted fludarabine–melphalan conditioning prior autologous stem cell transplantation in a dialysis-dependent patient with mantle cell lymphoma

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Dear Editor,

High-dose (HD) chemotherapy with autologous stem cell transplantation (SCT) has demonstrated to improve the outcome of relapsed aggressive non-Hodgkin lymphoma (NHL) and represents the current option of choice in suitable patients although it is associated with considerable acute and chronic toxicities [1]. In patients with renal failure, the treatment approach to aggressive NHL has not been stated. Moreover, conditioning regimens prior autologous SCT generally include HD of agents, which are contraindicated in the presence of severe renal impairment. Therefore, the application of myeloablative treatments to this category of frail patients remains a challenging concern.

The case of a patient submitted to autologous SCT following conditioning with adjusted doses of fludarabine and melphalan (Flu/Mel) is here reported together with the description of the dialysis regimen adopted during the transplantation procedure. A 69-year-old male presented a second relapse of [AU1]mantle cell lymphoma after a 3-year maintained complete remission (CR). He received the rituximab, dexametazone, cisplatin and high doses of

cytarabine (R-DHAP) regimen as salvage treatment. Unfortunately, during the first course of HD chemotherapy, he developed severe and unrecoverable renal impairment due to cisplatin toxicity for which he required dialysis on regular basis. The treatment resulted in a CR, as demonstrated by a body computed tomography scan and by bone marrow trephine biopsies. However, given the high risk of relapse, autologous SCT as consolidation was offered.

The patient was properly informed and gave his consent. Therefore, 2 months after the completion of HD chemotherapy, stem cells were then regularly mobilized and collected after adjusted doses of intravenous (IV) cyclophosphamide (3 g/m^2 , day +1), followed by daily filgrastim ($5 \mu\text{g kg}^{-1} \text{ day}^{-1}$ from day +5). After the stem cell collection, the patient was soon transplanted. Flu/Mel regimen was administered as conditioning at adjusted doses according to the dialysis-dependent renal failure and the patient's low performance status (Karnofsky score of 60%). Therefore, he received IV fludarabine at the dose of $6 \text{ mg m}^{-2} \text{ day}^{-1} \times 4$ days followed by IV melphalan 100 mg/m^2 the fifth day of the conditioning phase.

Stem cell dose was 4.3×10^6 CD34-positive cells per kilogram. Antifective prophylaxis included the daily administration of standard doses of levofloxacin and itraconazole and a reduced dosage (50%) of acyclovir. Dialysis procedures were performed daily during the conditioning phase and then thrice a week. Engraftment was achieved at day +12 for absolute neutrophil count $>0.5 \times 10^9$ and +15 for platelet count $>20 \times 10^9$. During the aplasia, the patient experienced an episode of febrile neutropenia for which he received piperacillin/tazobactam and teicoplanin, which, compared to the standard, were

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reduced to one third and one half, respectively. Mucosal toxicity was mild (WHO grade 1 mucositis) and no other complications were recorded.

To date, 16 months after autotransplantation, the patient is alive and in CR; no changes were observed in dialysis requirement. Although Flu/Mel is a highly effective reduced intensity conditioning regimen prior allogeneic SCT [2], its application has not been reported so far in the autologous setting. On the basis of the few reported evidences on its pharmacokinetic in dialysed patients [3, 4], compared to the reported standard Flu/Mel (fludarabine 25 mg/m² iv daily from day -6 to day -2) and melphalan (90 mg/m² iv on days -3 and -2) in the allogeneic setting [2], a reduction of about 75% and one third of the doses of fludarabine and melphalan, respectively, were adopted. Given his low performance status and in order to avoid severe toxicity, above all in the form of mucosal injuries, our patient received a reduced dosage of melphalan compared to the standard dose, according to previously reported on patients with multiple myeloma and renal dysfunction submitted to autologous SCT [5].

This is the first report on ASCT performed in NHL with end-stage renal failure. Our experience outlines the feasibility of Flu/Mel regimen in patients with dialysis depending renal failure. Although we adopted several interventions and modifications of the standard measures on empirical clinical basis, they seemed adequate. Other than the feasibility, the favorable clinical result we achieved in a frail and high-risk patient was indirectly suggested by his relatively long-term follow-up. However, given that high

caution should be required to draw any conclusion on the effectiveness of this treatment strategy from the outcome of a single patient, we conclude that well-designed clinical trials, in close collaboration with nephrologists, are urgently awaited in order to establish firm guidelines and a rationale treatment approach to poor prognosis NHL patients with renal failure.

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