Is it time to discontinue using high-dose chemotherapy for salvage of patients with advanced germ-cell tumors failing first-line platinum chemotherapy?

We read with interest the article by Pico et al. [1]. In their report, it was stated that a single cycle of high-dose chemotherapy (HDT) after three cycles of standard dose chemotherapy had no effect on treatment outcomes of patients with advanced germ-cell tumor failing first-line platinum chemotherapy compared with four cycles of standard dose chemotherapy. The authors stated that ‘these results suggest that data from uncontrolled studies should not be used to justify routine use of a toxic and expensive treatment without confirmation in a randomized trial.’ Although we agree with the comment by Pico et al. based on their valuable study, currently it does not appear reasonable to conclude that HDT is not an effective approach for the following reasons.

(i) Paclitaxel–ifosfamide–cisplatin (TIP) combination therapy seems to lead to higher response rates compared with VeIP (vinblastine–etoposide–cisplatin) and cisplatin–etoposide–ifosfamide (PEI) [2]. So, administration of TIP in pretransplant setting may lead to lower tumor burden and this may increase efficacy of HDT.

(ii) In Pico et al.’s study, although 280 patients were assigned for the treatment, only 96 patients in the HDT group could receive the scheduled therapy and 103 patients in the standard dose chemotherapy arm could complete the whole schedule. So although no significant difference was observed in 3-year event-free survival (EFS) ($P = 0.16$), this could be due to the study being underpowered to answer this survival end point. Recruiting more patients could have lead to a significant improvement in EFS.

(iii) Pico et al. showed in a subgroup analysis that among patients achieving a complete response (CR) to HDT, 2-year disease-free survival (DFS) was significantly improved. Although this analysis was not planned in advance, we think this is a significant finding, with a 20% difference in 3-year DFS rates, showing a benefit of autologous stem cell transplantation (ASCT) if CR can be achieved. Thus, CR achieved with VeIP/PEI was not durable, while CR in the HDT arm was long-lasting. Although overall survival (OS) rates in this subgroup analysis were not mentioned in the text, this DFS difference may be a predictor of OS. Therefore, any effort to increase the CR rate achieved should be undertaken for better outcome, and this may be achieved by incorporating paclitaxel, by tandem transplants or by giving highest doses of chemotherapeutics with a sequential approach.

(iv) Recently, tandem high-dose chemotherapy with autologous stem cell support has been a promising approach in germ-cell tumors [3, 4]. Although its efficacy over single ASCT has not been studied, this can lead to better results owing to enhanced consolidation following cytoreduction by the first prior HDT protocol.

(v) Several subgroups that have poor prognosis despite use of ASCT have been defined. These are patients with primary mediastinal germ-cell tumor and with Beyer score >2 [5–7]. Patients with primary mediastinal germ-cell tumor have a 2-year failure-free survival rate ranging between 0% and 12%, while those patients with a Beyer score >2 have a 2-year DFS of 5% and 2-year OS of 8% with HDT. Therefore, these patients should be excluded from future studies.

We believe that more research effort is definitely needed before drawing a conclusion about the efficacy of HDT in advanced germ-cell tumors refractory to cisplatinum-based first-line chemotherapy. We need randomized prospective trials to find the answers to several questions, but this will not be easy when we take in consideration that platin-refractory germ cell tumors are not common.

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