Multiple myeloma (MM) is a plasmocytic malignancy which accounts for approximately 10% of all hematologic malignancies. In 2016, over 16,500 new cases were diagnosed in China, and approximately 10,300 patients died of the disease.\(^1\) In novel-agent era, some patients had a poor prognosis with a median overall survival (OS) of <2 years although they received the therapy regimen containing novel agents and autologous peripheral blood stem cell transplantation (APBSCT) as front-line therapy.

Stratification for Myeloma and Risk-Adapted Therapy 3.0 (mSMART 3.0) from Mayo Clinic is a risk-stratification guideline revised in 2020.\(^2\) This risk-stratification guideline proposed a novel point of view as having two of the above genetic abnormalities to be named as double-hit MM and having any three or more as triple-hit MM. However, we have not known whether APBSCT as front-line therapy could reverse the poor prognosis of myeloma with double-hit or triple-hit in novel-agent era. So, we aimed to evaluate the role of APBSCT for MM patients with double-hit and triple-hit in real-world.

We reviewed the medical records of patients with newly diagnosed MM (NDMM) who received APBSCT as front-line therapy after induction therapy in Beijing Chao-Yang Hospital (Beijing, China) from January 2010 to December 2019. Finally, 240 patients were enrolled in the study. The demographics and disease-related characteristics at diagnosis were summarized and checked by no less than two different researchers in the study. Interphase fluorescence in situ hybridization (iFISH) analysis was performed on a treat-naïve bone marrow specimen at diagnosis. Induction regimens included at least one novel agent, including proteasome inhibitors (bortezomib) and immunomodulators (thalidomide and lenalidomide). High-dose therapy and APBSCT constituted front-line therapy for all the patients in our study. Most of the patients received maintenance therapy from day 100th after APBSCT. Response was estimated for all the patients after induction therapy and at day 100th after APBSCT, respectively. All the patients were followed up and the last follow-up time was April 30, 2020. To analyze the role of APBSCT as front-line therapy for myeloma with double-hit or triple-hit, we reviewed some published data\(^3,4\) and compared our results with them. Statistical analysis was conducted using SPSS 22.0 software (SPSS, Chicago, IL). A two-sided \(P\) value < 0.050 was considered to be of statistical significance.

Based on iFISH analysis results, 110 patients did not have any high-risk cytogenetic abnormalities (standard-risk subgroup, \(n=110\)), 96 patients had one high-risk cytogenetic abnormality (high-risk subgroup, \(n=96\)), 31 patients had two high-risk cytogenetic abnormalities (double-hit), and three patients had three high-risk abnormalities (triple-hit). Because there were fewer patients with triple-hit, we combined patients with double-hit and patients with triple-hit into a single subgroup for further analysis (double-hit and triple-hit subgroup, \(n=34\)).

All the patients received median four cycles of induction therapy (range 2–13) and at least one novel agent was contained in the induction regimens. The proteasome inhibitor bortezomib was widely adopted during induction therapy and the rate reached to 90.0% (216/240). There was no statistic difference on induction regimens among the subgroups (\(P=0.321\)). The subgroups had similar data in terms of high-dose therapy regimen before APBSCT.
After median four cycles of induction therapy (range 2–13), the deeper response rate (≥ very good partial remission) in the study was 71.7% (172/240) and the different subgroups had similar results (standard-risk vs. high-risk vs. double-hit and triple-hit, 70.0% vs. 75.0% vs. 67.6%, P = 0.149). At day ~100th after APBSCT, the deeper response rate was 84.6% and the subgroups had no difference (standard-risk vs. high-risk vs. double-hit and triple-hit, 82.7% vs. 84.5% vs. 79.5%, P = 0.070). At the same time, 73/240 (30.3%) got further remission in the study and there was no difference among the subgroups (P = 0.106).

After a follow-up of median 33.5 months (range 12–132 months), median progression-free survival (PFS) was 41 months and median OS was 89 months for the whole. Median PFS of the patients in double-hit and triple-hit subgroup was much shorter than other subgroups (standard-risk vs. high-risk vs. double-hit and triple-hit, 82 vs. 33 vs. 28 months, P < 0.001). Median OS of the patients in double-hit and triple-hit subgroup was much shorter than other subgroups (standard-risk vs. high-risk vs. double-hit and triple-hit, 107 vs. 70 vs. 44 months, P < 0.001). iFISH: Interphase fluorescence in situ hybridization; OS: Overall survival; PFS: Progression-free survival.

Multivariate analysis of PFS and OS was performed. High-risk, double-hit and triple-hit, Immunoglobulin A/Immunoglobulin lambda, International Staging System stage II–III, extramedullary disease, and no-sCR (stringent complete remission) at day 100th after APBSCT were associated with shorter PFS, especially high-risk (hazard ratio [HR] = 3.444, 95% confidence interval [CI]: 2.130–5.571, P < 0.001) and double-hit and triple-hit (HR = 5.146, 95% CI: 2.832–9.349, P < 0.001). Further remission at day 100th after APBSCT was an independent favorable factor for longer PFS (HR = 0.428, 95% CI: 0.276–0.662, P < 0.001). High-risk, double-hit and triple-hit, serum creatinine ≥177 μmol/L, extramedullary disease, and no-sCR at day 100th after APBSCT were associated with shorter OS, especially high-risk (HR = 2.908, 95% CI: 1.539–5.493, P = 0.001) and double-hit and triple-hit (HR = 5.549, 95% CI: 2.532–11.715, P < 0.001). Further remission at day 100th after APBSCT was an independent favorable factor for longer OS (HR = 0.386, 95% CI: 0.216–0.688, P = 0.001).

Figure 1: Kaplan-Meier Curves of PFS (A) and OS (B) in the different subgroups based on iFISH. After a follow-up of median 33.5 months (range 12–132 months), (A) median PFS of the patients in double-hit and triple-hit subgroup was much shorter than other subgroups (standard-risk vs. high-risk vs. double-hit and triple-hit, 82 vs. 33 vs. 28 months, P < 0.001) and (B) median OS of the patients in double-hit and triple-hit subgroup was much shorter than other subgroups (standard-risk vs. high-risk vs. double-hit and triple-hit, 107 vs. 70 vs. 44 months, P < 0.001).
disease control for patients with high risk cytogenetic abnormalities. Perhaps, such patients with MM could get a survival benefit from tandem transplantation.

In summary, MM patients with double-hit and triple-hit had a seriously poor prognosis and novel agents available cannot effectively delay disease progression. APBSCT should be the front-line therapy for MM patients with double-hit and triple-hit even in novel-agent era, because APBSCT might partly overcome the poor prognosis of the patients with double-hit and triple-hit compared with chemotherapy. It is essential to research the disease biology of myeloma with double-hit and triple-hit.

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**Conflicts of interest**
None.

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