Clinical characteristics and survival of patients with IgD multiple myeloma

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MM (multiple myeloma) accounts for about 10% of hematological malignancies and 1% of cancer. IgD myeloma is a rare type of MM. It was reported that IgD type accounts for about 1% to 2% of all patients with MM abroad, while 3% to 8.9% in domestic cases.[1] This immunoglobulin protein was first discovered by Dr. Rowe and Fahey in 1965.[2] Half of a century had passed, the management of IgD MM remains a challenging field. As the secretion of IgD is low in the serum, monoclonal protein of IgD is difficult to confirm by serum protein electrophoresis or immunofixation electrophoresis. Recently, Wang et al[3] showed that detection of cytoplasmic IgD by flow cytometry is a sensitive way to diagnose patients with IgD myeloma. Clinical cases of IgD myeloma are usually more aggressive and manifest high-risk features (severe complications and comorbidity, younger age, high incidence of extramedullary infiltration, bone destruction, hypercalcemia and renal insufficiency, genetic abnormalities, etc) when compared with other subtypes of MM.[4]

Studies on IgD type of myeloma is limited given the rarity of large-scaled clinical data. In 2019, Selene et al[5] made a systemic review in 5 different databases from 2013 to 2018. Their work summarized the presentation patterns, management, and prognosis factors of 166 patients with IgD MM. As this type was more common in Asian population, we could see a serios studies focus on in Asia and Southeast Asia. Lu et al[6] summarized 61 cases in 940 newly diagnosed MM patients and found that patients younger than 50 years old were more likely with IgD subtype (10.3% vs 5.5%, $P = .015$), as a poor prognostic factor. Hu and coworkers[7] identified 47 patients with IgD myeloma in single center. The results showed that IgD type was more common in Chinese population (7.5%), with special characteristics: more male predominant, higher tumor burden, higher frequency with IgH translocation, and the prognosis could benefit from the use of new drugs and ASCT. We read with great interest the report by the AMN cohort,[1] the largest retrospective study to date, included 356 patients with IgD myeloma from three different countries in Asian. The results represent the incidence of IgD type in Asian population and showed these patients had a higher frequency in male, younger age, advanced stage (ISS staging system), hypercalcemia, high tumor burden and renal dysfunction, which is in accordance with former studies.

Cytogenetic changes play an important role in the pathogenesis of MM. Previous studies had showed more frequent of genetic aberrations in IgD type myeloma. Results by Liu and coworkers[8] demonstrated that 15 cases (78.9%) were normal karyotype, and 4 cases (21.1%) were complex karyotype in all assessable 19 patients. 18 cases (90%) had TP53 gene deletion and/or 1q21 amplification, and all of them were complicated with more than two kinds of genetic abnormalities. It is considered that lq21 amplification is one of the poor prognostic factors in IgD MM,[9] which was confirmed by some single center studies, suggesting high-risk inheritance of IgD subtype. Hu and coworkers[7] showed the median PFS and OS of 47 patients with IgD myeloma carried the 17p- was significantly shorter than patients without the deletion. Translocation of t (4;14) was strongly associated with inferior OS and PFS. These studies were all based on small population. We could suspect the risk stratification system for IgD myeloma, as a type of poor prognosis myeloma, maybe different from non-IgD subtypes.

It is noteworthy that the AMN cohort reported by Du and coworkers[1] summarized the cytogenetic information in 301 (84.6%) patients and 40.6% of patients with abnormal karyotypes. The expression of del 13q, 1q21 amp, t (11:14), t (4;14) and double hit detected by FISH in plasma cells were significantly different in IgD and non-IgD patients ($P \leq .001$). Del (17p-) is a high-risk factor in myeloma, but with no significant difference ($P = .609$) from the report of AMN. As shown in their report, t (11;14) was detected more frequently in IgD MM when (29%) compared to that in non-IgD subtypes ($P < .001$), usually coupled with some other high-risk factor such as 13q-, 1q21+, and 17p-. This was consistent with previous work and verified with more clinical cases. It is known that t (11;14) was not a high-risk cytogenetic change in myeloma, but why this translocation is often associated with advanced disease in IgD subtype remains unclear. As tumor cells harboring t (11;14) were associated with high expression of bcl-2, bcl-2 inhibitor venetoclax might provide a new option for these patients. Some report[10] showed that the monoclonal plasma cells of IgD are not derived from the transformation of stem cells or pre-B cells but are formed by extensive hypermutation in the variable region of immunoglobulin heavy chain secreted by B cells in the germinal center. These may explain the cytogenetic aberrations is different in IgD myeloma with non-IgD type, but still need further research.

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Compared with other subtypes, the median survival of patients with IgD type received traditional chemotherapy is generally less than 2 years.[4] Studies have shown that combined with autologous hematopoietic stem cell transplantation, the use of proteasome inhibitors, immunomodulatory agents could significantly improve the prognosis of patients.[7,11] Analyzing the impact of novel agents on the outcome of patients with IgD subtype, Du and coworkers[1] showed that patients received IMiDs appeared to be associated with a better median OS than other regimens. However, this was not statistically significant ($P = .17$). This may be due to patients with IgD type often harbor complicated genetic aberration, which could not be converted by IMiDs. Others such as new generation of immunomodulator (Pomalidomide), proteasome inhibitors (carfilzomib, ixazomib), histone deacetylase inhibitors (panobinostat, vorinostat), monoclonal antibodies (daratumumab, elotuzumab) and kinds of immunotherapies have proved to provide innovative therapies for MM. These new agents may be promising in the treatment of patients with IgD subtype but have not been verified in clinical trials.

IgD type itself is an adverse prognosis factor in myeloma. For lacking evaluable cases, previous studies usually concentrated on the prognostic value of single variable, such as serum free light chain ratio,[12] serum IgD,[13] serum IgD quantification plus serum FLC levels,[13] bone marrow plasma cytosis,[14] N glycan peak[15] are evaluable prognosis factors ($P < .005$), but 1q21 amp was not with poor survival[14] in one retrospective study. Du and coworkers[1] constructed a comprehensive prognostic model based on the multivariate LASSO Cox regression model of multi variables. Light chain ratio of plasma cells in BM, anemia, LDH and extramedullary plasmacytoma were identified clinically relevant to identify high risk patients. This innovative work may improve the classification of IgD myeloma and facilitate the development of risk-adapted treatment strategies. However, cytogenetic changes were not involved in this model, which still needs to be verified by multi-center studies.

IgD MM is a rare myeloma subtype associated with a more aggressive disease and inferior survival. The reports from AMN cohort firstly identified IgD subtype of MM was much more common in the Asian population by multi-center analysis. Patients received IMiDs seemed to have prolonged median OS than other regimens (did not reach statistically significance), which is important in the era of novel agents. Their work showed the IgD subtype has special characteristics in cell biology and cytogenetics, which requires a unique risk stratification for adapted therapy. Most of all, the new prognostic model proposed by Du and coworkers[1] may provide novel concept for the treatment of patients with IgD subtype MM.

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