MultipleMyelomaHub

Relapsed/refractory patients

Impact of acquired del(17p) in multiple myeloma

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An adverse prognostic effect can be observed in patients with multiple myeloma (MM) who exhibit the abnormality del(17p). This is ordinarily detected via fluorescence *in situ* hybridization (FISH) on malignant bone marrow plasma cells (PCs) in approximately 10% of patients with relapsed/refractory (R/R) MM, and can result in reduced overall survival (OS).

Despite improvements in the understanding of disease biology and novel therapeutic approaches, the outcomes of patients who acquire del(17p) are not known. Patients acquire del(17p) through the deletion of (or a portion of) chromosome 17p, and could be due to selection pressures from treatment.

Arjun Lakshman, from Mayo Clinic, Rochester, US, and colleagues aimed to assess the impact of the acquisition of del(17p) (cases) on the survival of patients by comparing them with control patients who did not acquire this deletion (controls).

Study design

Eighty patients with MM and acquired del(17p) were identified from the dysproteinemia database at Mayo Clinic, Rochester, US. All patients were negative for del(17p) on an initial FISH analysis, but the abnormality was later detected on a follow-up FISH analysis between 2004 and 2016. Of the 80 patients, 76 who had R/RMM were included in the study.

FISH analysis:

- 57 (75%) patients had initial FISH analysis within 6 months of MM diagnosis
- 19 (25%) had initial testing after 6 months of MM diagnosis

For each case, two control patients were identified who were diagnosed during the same time period, but did not demonstrate del(17p) during follow-up (n=152). Control patients had a minimum of two negative FISH analysis, with the second test occurring at a similar or later time point to the timing of del(17p) detection in the respective cases. Survival outcomes in the acquired del(17p) group were also compared to a separate cohort of patients (n=310) with del(17p) detected at diagnosis (*de novo* del(17p)).

Responses to treatment were defined using the 2016 Revised International Myeloma Working Group Criteria.[1]

Cytospin slides were prepared using bone marrow aspirate samples enriched for mononuclear cells. FISH analysis was performed using the following probes:

- *D3Z1*

- *D7Z1*
- *LAMP1*
- *p53*
- *D17Z1*
- *IGH-XT*
- *3'IGH,5'IGH*
- *FGFR3*
- *c-MAF*
- *CCND3*
- *MAFB*
- *TP73*
- *1Q22*

A test was considered positive if 7% of cells exhibited del(17p13.1) or if 9% cells demonstrated monosomy 17.

Patient characteristics

Cases and controls had similar baseline characteristics and initial treatments. In comparison to controls, cases had a higher predominance of elevated lactate dehydrogenase (LDH; 13.7% *vs* 4.1%, p= 0.043), a higher occurrence of translocation (4;14) (15.8% *vs* 6.6%, p= 0.033), and relatively low hemoglobin at diagnosis (median, 10.8g/dL *vs* 11.3g/dL, p= 0.035).

In the *de novo* group, 47.4% patients were ≥ 65, with 23.8% having elevated LDH, more than 95% initially being treated with novel agents, and 56% receiving stem cell transplantation at any time during their disease course.

Key findings

Patient characteristics at del(17p) detection

- Median time from diagnosis of MM to detection of del(17p) in acquired del(17p) was 35.6 months (4.8–116.1)
- Median of 2 (1–10) prior lines of therapy
- 67.1% patients exposed to a proteasome inhibitor (PI), 39.5% PI refractory
- 92.1% patients exposed to an immunomodulatory drug (IMiD, majority lenalidomide/pomalidomide), 39.5% IMiD refractory
- 78.9% patient exposed to an alkylating agent, 32.9% refractory to an alkylating agent
- 86.8% patients had del(17p13.1)
- 6.6% patients had monosomy 17
- One patient had both del(17p13.1) and monosomy 17 (deletions of p region on both copies of chromosome 17)
- The number of patients with hyperdiploidy increased at detection of del(17p) (42.1% *vs* 59.2%; p< 0.001)

Patient outcomes

Table 1: OS and PFS in patients in the study groups

	Control	Acquired del(17p)	*de novo* del(17p)
PFS (months)	30.1	23	21.2
OS (months)	106.1	68.2	47.3

IMiD- and PI-based regimens were used in 22 patients, an IMiD+PI regimen was used in 15 patients, and monoclonal antibodies were used in four patients. Six patients received other therapies, and seven proceeded directly to stem cell transplantation. Of the 67 patients evaluated, three achieved stringent complete response, 3 attained complete response (CR), 16 very good partial response, and 9 achieved partial response. The OS rate was 46.3%, and median OS from detection of del(17p) was 18.1 months (95% CI, 11.9–25).

Age, serum creatinine levels, bone marrow PC percentage, ISS stage, LDH, presence of high-risk translocations (HRT), monosomy 13, hyperdiploidy, PC proliferative rate, prior IMiD and PI were used to predict survival outcomes after the detection of del(17p). High LDH at baseline, the presence of t(4;14) and the presence of any HRT predicted the acquisition of del(17p).

Conclusions

In R/R MM, detection of del(17p) at diagnosis or in follow-up, is associated with a reduction in OS. The results of this study were used, with other factors, to predict survival outcomes for patients who acquired del(17p). The association with high LDH, HRTs, and shorter PFS in first-line therapy may suggest that patients who acquire del(17p) have an aggressive biology, even at diagnosis. This could be helpful when designing clinical trials for patients with acquired high-risk disease.

References

1. Kumar, *et al*., Dimopoulos M. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. The lancet oncology. 2016 Aug 1;17(8):e328-46. DOI: 10.1016/S1470-2045(16)30206-6
2. Lakshman A., *et al*., Impact of acquired del (17p) in multiple myeloma. Blood Advances. 2019 Jul 9;3(13):1930-8. DOI: 1182/bloodadvances.2018028530