Table 1 Clinical characteristics of patients with *NF1* mutation-positive acute leukemia

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Patients’ clinical characteristics |  | ALL(n=12) | AML(n=15) | APL(n=1) |
| Sex: Male/Female |  | 7:5 | 2:1 | 0:1 |
| Age: |  | 7(3.3-14.8) | 11(0.6-15.4) | 8 |
| Chromosomal karyotype |  |  |  |  |
|  | Normal karyotype | 10(83.3%) | 13(86.6%) | 1(100%) |
|  | Hyperdiploid | 2(16.7%) | 0 | 0 |
|  | -7 | 0 | 1(6.7%) | 0 |
|  | t(7; 11)(p15; p15) | 0 | 1(6.7%) | 0 |
| Level of risk |  |  |  |  |
|  | Low risk | 1(8.3%) | 3(20.0%) | 1(100%) |
|  | Intermediate risk | 9(75.0%) | 2(13.3%) | 0 |
|  | High risk | 2(16.7%) | 10(66.7%) | 0 |
| Treatment protocols |  |  |  |  |
|  | Targeted drugs | 3(25.0%) | 7(46.7%) | 0 |
|  | Transplantation | 0 | 9(60.0%) | 0 |

Table 2 Genes, MRD and survival of patients with *NF1* mutation-positive ALL

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| No. | Level of Risk | Gene Mutations | Gene Fusion | Treatment Methods | D15 MRD | D33 MRD | Current Condition |
| ALL-1 | Intermediate risk | No | No | Chemotherapy | 6.2×10^-2 | 5.0×10^-4 | In chemotherapy |
| ALL-2 | Low risk | *IKZF1, KMT2C, ASXL3, SMC1A* | No | Chemotherapy | - | 1.32×10-6 | Drug withdrawal for one year |
| ALL-3 | Intermediate risk | *TP53, RB1, PIK3CD, USH2A* | No | Chemotherapy | 1.0×10-3 | Negative | In chemotherapy |
| ALL-4 | High risk | *INRAS, KRAS, CSMD1, SOS1* | No | Chemotherapy | 3.0×10^e-3 | 2.1×10e-4 | In chemotherapy |
| ALL-5 | Intermediate risk | *CREBBP, KRAS, IRF8, TBL1XR1* | *SPI1::ZNF384* | Chemotherapy + blinatumomab | 2.0×10^e-2 | 8.0×10^e-5 | In chemotherapy |
| ALL-6 | Intermediate risk | *NRAS, FLT3, IKZF3* | *DUX4::lgHJ6(582)* | Chemotherapy | 5.5×10^e-3 | Negative | In chemotherapy |
| ALL-7 | Intermediate risk | No | No | Chemotherapy | 1.0×10^e-4 | Negative | In chemotherapy |
| ALL-8 | Intermediate risk | *FLT3, PTPN11, KRAS, ETV6* | *EP300-ZNF384* | Chemotherapy | 7.2×10e-3 | 4×10^e-5 | In chemotherapy |
| ALL-9 | Intermediate risk | *NRAS, KRAS* | No | Chemotherapy | 2.2×10^e-3 | Negative | In chemotherapy |
| ALL-10 | High risk | *NRAS, KRAS, CREBBP* | No | Chemotherapy + blinatumomab | 1.3×10^e-2 | Negative | In chemotherapy |
| ALL-11 | Intermediate risk | No | *TEL-AML1* | Chemotherapy | 5.8×10^e-3 | 4×10^e-5 | In chemotherapy |
| ALL-12 | Intermediate risk | *ASXL1, ATRX, CHD2* | *EP300-ZNF384* | Chemotherapy | 2.0×10^e-4 | Negative | In chemotherapy |

Table 3 Genes, MRD and survival of patients with *NF1* mutation-positive AML + APL

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| No. | Regimens | Level of Risk | Gene Mutations | Gene Fusion | Treatment Method | D21 MRD | D28 MRD | Current Condition |
| AML-1 | CCLG-2019 | High risk | *PTPN11* | *KMT2A-MLLT3, MLL-AF9* | Chemotherapy + venetoclax | Bone marrow no response | - | Died due to severe infection after chemotherapy |
| AML-2 | CCLG-2015 | High risk | *GATA2, WT1* | *NUP98-HoxA9* | Chemotherapy + transplantation | 9.36×10-3 | 2.609×10-3 | Relapsed and died 3 years after transplantation |
| AML-3 | CCLG-2019 | High risk | No | No | Chemotherapy + venetoclax + transplantation | 4.67×10-2 | 7.72×10-2 | Died after transplantation |
| AML-4 | CCLG-2019 | High risk | No | No | Chemotherapy + venetoclax + transplantation | - | Negative | In transplantation |
| AML-5 | CCLG-2019 | High risk | *IDH2, NRAS, WT1* | No | Chemotherapy + venetoclax + transplantation | 6×10-4 | 9×10-4 | One year after transplantation |
| AML-6 | CCLG-2019 | Intermediate risk | *IDH1, NPM1, PTPN11* | *Low-level FLT3-ITD* | Chemotherapy + venetoclax + gilteritinib | Negative | Negative | In chemotherapy |
| AML-7 | CCLG-2019 | High risk | No | No | Chemotherapy + venetoclax + transplantation |  |  | One year after transplantation |
| AML-8 | CCLG-2019 | Standard risk | No | *CBFβ-MYH11* | Chemotherapy | Negative | Negative | Drug withdrawal for three years |
| AML-9 | CCLG-2019 | High risk | *RUNX1, ASXL1, SETBP1, EZH2* | No | Chemotherapy + venetoclax + transplantation | 1.44×10^e-2 | 1.83×10^e-2 | One year after transplantation |
| AML-10 | CCLG-2019 | High risk | No | No | Chemotherapy + transplantation |  | 3.4×10-3 | Two years after transplantation |
| AML-11 | CCLG-2015 | Standard risk | *PHF6* | *AML1-ETO* | Chemotherapy | 2.694×10-3 | 4.3×10-4 | Drug withdrawal for five years |
| AML-12 | CCLG-2015 | Intermediate risk | *PTPN11* | No | Chemotherapy | 5.05×10-2 | 2.28×10-2 | Gave up and died after chemotherapy |
| AML-13 | CCLG-2015 | High risk | *WT1* | No | Chemotherapy + transplantation |  | Positive | Six years after transplantation |
| AML-14 | CCLG-2015 | Standard risk | *TP53* | *AML1-ETO* | Chemotherapy | 1.413×10-1 | 6.9×10-2 | Drug withdrawal for six years |
| AML-15 | CCLG-2015 | High risk | *c-KIT,TP53* | *CBFβ-MYH11* | Chemotherapy + transplantation | 2.43×10^-3 | 2.04×10-3 | Six years after transplantation |
| APL-1 | APL-2016 | Standard risk | No | *PML-RARA* | Chemotherapy | Negative | 5.87×10-2 | Drug withdrawal for three years |

Table 4 Summary of the symptoms of patients with neurofibromatosis and their *NF1* gene loci

|  |  |  |  |
| --- | --- | --- | --- |
| No. | Clinical Symptoms | *NF1* Gene Variation Loci (Variation Frequency%) | Somatic/Germline Validation |
| ALL-1 | CALM, scoliosis, intracranial involvement | *exon3: c.247C>T(p.Q83\*)(70.2%)* | Germline |
| ALL-2 | CALM, xanthogranuloma, intracranial involvement | *exon38(c.5749+5G>A)* | Germline |
| ALL-3 | CALM, scoliosis, intracranial involvement | *exon44:c.6733C>T:p.Q2245X(36.8%)* | Somatic |
| ALL-4 | No | *exon28:c.3827 G>A:p.R1276Q(3.6%)* | Somatic |
| ALL-5 | No | *exon2:c.128\_147delinsAACGG:p.L43\_Y49delinsQR(4.8%)*  *c.205-10\_231delinsGACGGCCAGGCCAG (7.6%)*  *exon18:c.2033dup:p.I679fs\*21 (8.2%)* | Somatic |
| ALL-6 | No | *exon18:c.2206\_2208delinsGCCACTCCTGGGG:p.N736fs\*35(27.1%)*  *exon41:c.6206\_6207insTGGGACGCATG:p.N2070fs\*24(28.0%)* | Somatic |
| ALL-7 | CALM | *exon20:c.2334\_2336dup:p.E778dup (82.8%)* | Somatic |
| ALL-8 | No | *exon10:c.1074dup:p.N359X (8.8%)* | Somatic |
| ALL-9 | No | *exon41:c.6185G>A:p.R2062H (13.1%)* | Somatic |
| ALL-10 | No | *exon12:c.1391C>T:p.P464L (8.9%)*  *exon34:c.4537C>T:p.R1513X (71.9%)* | Somatic |
| ALL-11 | No | *exon17:c.1996\_1997insAGGCTACC:p.S666X (17.3%)* | Somatic |
| ALL-12 | No | *exon48:c.7153\_7154insGGCCTG:p.I2384\_V2385insGP(2%)* | Somatic |
| AML-1 | No | *c.2033C>T(35.9%)* | Germline |
| AML-2 | CALM | *c.1933A>G(47.7%)* | Germline |
| AML-3 | No | *c.888+5G>A(51.99%)* | Germline |
| AML-4 | No | *c.6007-1G＞C(1.9%)*  *c.6855C＞A p.Tyr2285Ter(1.8%)* | Somatic |
| AML-5 | No | *c.6927\_6941delinsCCCAGA(30%)* | Somatic |
| AML-6 | No | *c.3168\_3169ins(16.7%)* | Somatic |
| AML-7 | No | *c.2033dup(21.4%)* | Somatic |
| AML-8 | No | *c.4676G>A(87.7%)* | Somatic |
| AML-9 | No | *exon18:c.2033dupC:p.I679fs\*21 (78.9%)* | Somatic |
| AML-10 | No | *c.1885G>A(35.12%)* | Somatic |
| AML-11 | CALM, freckles | *c.910C>T(39.2%)* | Somatic |
| AML-12 | No | *c.5902C>T(37.84%)* | Somatic |
| AML-13 | No | *c.654+44A>C(50.65%)* | Somatic |
| AML-14 | No | *c.730+48A>G(54.66%)* | Somatic |
| AML-15 | No | *c.6921+40A>G(54.08%)* | Somatic |
| APL-1 | No | *c.6427+10A>G(50.3%)* | Germline |