

discovered that, in assays of PBMC blasts, an increase that was under 5×10^{-4} was associated with a longer time to relapse, while an increase above 5×10^{-4} was associated with a shorter time to relapse (median 27 days to relapse) (Fig. 18.3).

The authors concluded that this assay method enabled detection of patients with poor prognosis, and in need of more aggressive therapy.

b. Example of Use of MRD and EFS— The Basso Study of Philadelphia Chromosome-Negative ALL

In a study of childhood ALL (Ph-negative ALL), Basso et al. (303) stratified patients according to MRD data that were collected from bone marrow samples on day 15 of the study. The MRD data were combined with established cytogenetics parameters, and this combination was used to define the following risk groups:

1. *High risk.* $t(4;11)(q21;q23)$ or $MLL/AF4$, and testing positive for MRD, where blast counts were greater or equal to 10%. *MLL/AF4* refers to the fusion of *MLL* gene and *AF4* gene, a fusion product often found in infant ALL. The *MLL* gene is also known as *ALL1*, *HRX*, and *Hrx1* (304).
2. *Low risk.* Patients lacking the high-risk cytogenetics and testing negative for MRD, that is, where blast counts were under 0.1%.
3. *Intermediate risk.* Patients not meeting the criteria for high risk or for low risk.

All of the subjects were non-Philadelphia chromosome-positive. Chemotherapy was for

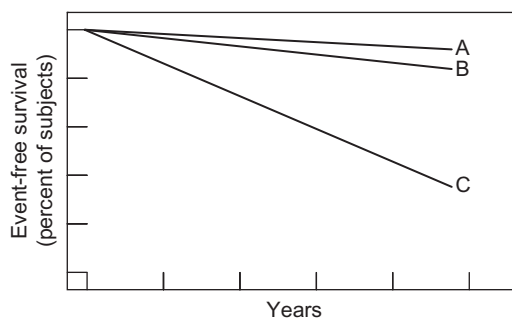


FIGURE 18.4 Schematic diagram of Kaplan–Meier plot of ALL. EFS is shown for patients stratified according to MRD. All patients received the same chemotherapy. At 15 days, bone marrow samples were withdrawn for use in MRD), where the results were used to define the three risk groups. The three strata were: (A) top line, under 0.1% blast cells; (B) middle line, between 0.1% and 10% blast cells; and (C) bottom line, greater or equal to 10% blast cells.

a 7-day period (days 1–7). The patients were followed for 5 years. The endpoint used in this clinical trial was EFS. EFS was a composite endpoint, that could be triggered by death, relapse, or by the appearance of a secondary malignant neoplasm. The Kaplan–Meier plot is schematically represented in Fig. 18.4.

The study found that where MRD was lowest (MRD under 0.1%), EFS data showed the most favorable outcome. The study also found that where MRD was greatest (MRD greater or equal to 10%), EFS data showed the worst outcome. The schematic diagram (Fig. 18.4) of the Kaplan–Meier plot discloses EFS for three different categories of patients.

EFS was used as an endpoint that was triggered by each individual patient, where results from individual patients are shown in the

³⁰³Basso G, Veltroni M, Valsecchi MG, et al. Risk of relapse of childhood acute lymphoblastic leukemia is predicted by flow cytometric measurement of residual disease on day 15 bone marrow. *J. Clin. Oncol.* 2009;27:5168–74.

³⁰⁴Cimino G, Cenfra N, Elia L, et al. The therapeutic response and clinical outcome of adults with ALL1(MLL)/AF4 fusion positive acute lymphoblastic leukemia according to the GIMEMA experience. *Haematologica* 2010;95:837–40.