

# Childhood Acute Lymphoblastic Leukemia: Differences in Drug Resistance between Sub-groups of ALL

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## **Abstract**

Acute lymphoblastic Leukemia (ALL) of Childhood nowadays has a cure rate of almost 75% in most western countries. Still, about 20% of patients relapse, or have initially resistant disease. Since long, risk factors are known that predict the prognosis. Relatively favourable indicators are: age between 1 and 10 years, lower white blood cell count (WBC), B-precursor immunophenotype, hyperdiploid chromosome number and TEL-AML1 translocation t(12;21). Unfavourable factors are either very young age or older age, WBC over 50,000 (and the higher the more unfavourable), MLL rearrangement and Philadelphia chromosome t(9;22). The reason for resistance to therapy may be found either in pharmacokinetics or in cellular drug resistance. If swift excretion of drugs, insufficient chemotherapy reaches the cells, and relapse is more frequent. If cellular resistance is present, even optimal (or maximal) chemotherapy will not kill off the leukemic cells. In the extreme case the malignant cells are more resistant to cytostatic drugs than normal cells of the patient, e.g. bone marrow and mucosa. In these cases intense treatment may kill the patient before the leukemic cells are eradicated. It has been shown extensively that in-vitro drug resistance tests show a clear correlation with the prognosis in ALL. Patients with resistance against the drugs, and especially with resistance to steroids, fare worse than patients with drug-sensitive cells. We routinely test ALL samples from initial blood or bone marrow against a panel of drugs. The data are correlated with the classical prognostic risk criteria. It appears that Infant ALL, most often also showing MLL rearrangement, is very resistant against most of the drugs used in ALL protocols, but is rather sensitive to ARA-C. This knowledge has helped designing the Interfant protocol. Older children and adults are more often in vitro resistant to steroids. The very good prognosis of hyperdiploid ALL goes together with in vitro sensitivity to anti-metabolites (6-MP, MTX) and to L-Asparaginase. ALL with TEL-AML translocation is likewise relatively sensitive to L-Asparaginase. In Philadelphia chromosome positive cases the pattern is not so clear in children. In adults Philadelphia positive cases are more resistant to steroids as compared to age- and immunphenotype matched non-Philadelphia positive cases. It is curious that WBC does not show a very clear correlation with the in vitro drug resistance pattern. Apparently, high tumor load is a risk factor on its own, that is not directly related to cellular drug resistance. The *in vitro* drug resistance test can be very useful for designing rational protocols for subgroups of patients. It can also be used for stratification of patients: those with a resistant pattern getting upgraded to more intensive therapy, those with sensitive in vitro results getting less intensive therapy. This option is now tested in ongoing clinical trials. In some relapse cases individual chemotherapy schemes can be chosen based upon, among other factors, the individual pattern of drug resistance of the relapsed ALL cells.

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