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Nelarabine – A New Age in the Management of Lymphoid Malignancies

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Nelarabine is the 6-methoxy pro-drug of 9- β -D-arabinofuranosyl-guanine (ara-G).¹ Nelarabine is a substrate for adenosine deaminase, which cleaves the methoxy group to form ara-G (Figure 1). Ara-G is taken up by the cell and is then triphosphorylated by two enzymes, deoxycytidine kinase and deoxyguanosine kinase² (Figure 2). Ara-G triphosphate (ara-GTP) competes with deoxy-GTP in malignant cells for incorporation into DNA.³ Once incorporation occurs, ara-GTP results in chain termination and apoptosis.² Ara-GTP accumulates to a greater extent in T-cells compared with B-cells. This may explain Nelarabine's greater activity in T-cell malignancies than B-lymphocyte malignancies. Elimination half-life of ara-GTP is longer in leukemic T-cells than in leukemic B-cells.⁴

Pharmacology and Pharmacodynamics

Nelarabine is given as an intravenous infusion. There is a direct proportionality of the area under the curve to the dose administered suggesting a one-compartment pharmacokinetic model.⁵ Nelarabine is rapidly deaminated by adenosine deaminase to form ara-G, a process which occurs in a period of one hour or less (Figure 1). Elimination half-life of ara-G in plasma is shorter in children than in adults being 2.1 hours in children and 3 hours in adults.⁵ Ara-GTP formation in T-cell ALL cells is significantly higher than in non-T leukemic cells.⁶ The purine analog fludarabine increases ara-GTP concentration presumably by increasing the activity of deoxycytidine kinase.⁷

Gandhi *et al.* have reported a clear relationship between ara-GTP accumulation and response in hematologic malignancies. The intracellular level of ara-GTP in responders was 3-4 times the level found in non-responders. There is a strong indication that the ara-GTP level is closely associated with

probability of response in all hematologic malignancies.⁶

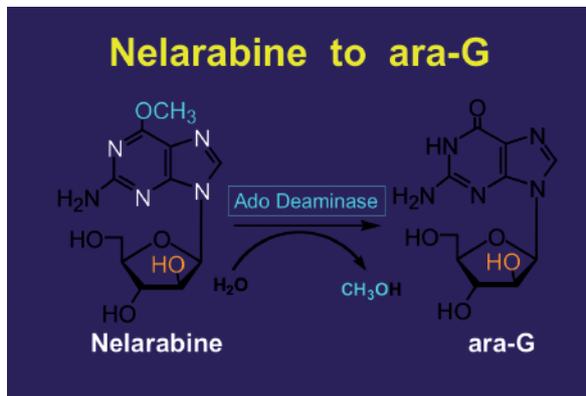
Clinical trials

The initial trial of nelarabine used a one hour infusion daily for five days. This study included both adults and pediatric populations with leukemias and lymphomas.⁸ Neurotoxicity was found to be dose-limiting at 75 mg/kg. The recommended maximum tolerated doses for adults was 40 mg/kg/day for five days and for children 60 mg/kg/day for five days. The courses were repeated approximately every four weeks. In the phase I dose escalation study, complete responses were noted and were more prominent in T-cell diseases. The complete response rate in T-cell disease for children was 7/26 (27%) and for adults 2/13 (15%). Partial responses were also seen in both adults and children (Table 1). Some of the responses were noted in other morphologic subtypes.

A trial conducted by the Southwest Oncology Group and Cancer and Leukemia Group B for T-cell ALL and T-cell lymphoblastic lymphoma was conducted.⁹ Forty patients were treated. The dose schedule was modified to 1.5 g/m² on days 1, 3, and 5. Twenty-one patients with ALL had a complete remission and 4/17 patients with T-cell lymphoblastic lymphoma. A phase II study was conducted at M.D. Anderson Cancer Center (MDACC) with 23 patients with peripheral T-cell lymphoma and 10 with indolent B-cell lymphomas.¹⁰ The same schedule as the preceding study of 1.5 g/m² intravenously on days 1, 3, and 5 was used with course repeated every 28 days was scheduled. Of 17 patients that were evaluable, two had a CR and six a PR.

Pediatric results

A clinical trial by Childrens Cancer Group and the Pediatric Oncology Group was conducted in refractory T-

**Table 1. Published clinical trials with nelarabine**

Clinical Trial	Disease	Patients	%CR	%CR+PR
Kurtzberg (8)	T-ALL/LBL	39	23	54
	CML-Blast	8	13	13
	Other	46	0	15
DeAngelo (9)	T-ALL	21	29	38
	T-LBL	17	24	24
Berg (11)	T-ALL	63	37	41
	T-NHL	22	0	14

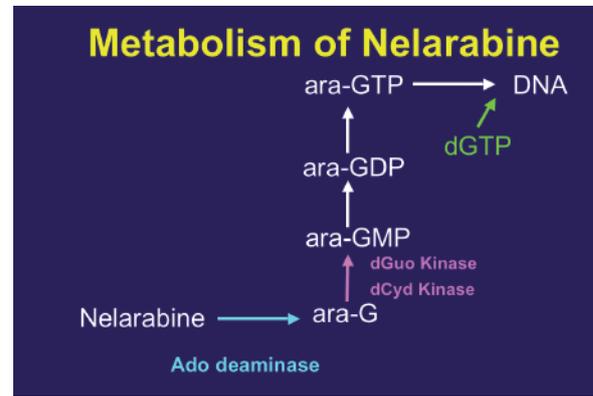
cell leukemias and lymphomas.¹¹ The responses were significantly higher in T-cell ALL. Forty-eight percent of 33 patients with T-ALL in initial relapse achieved a complete remission and 23% of 30 patients in second relapse.

Toxicity

Myelosuppression was not a major feature of nelarabine therapy. Neurologic toxicity was dose-limiting. Significant neurotoxicity was noted in the phase I dose escalation of Kurtzberg *et al.*⁸ Neurotoxicity was usually reversible and occurred more frequently in adults than in children. The neurotoxicity occurred in the first 1-2 weeks of therapy. A strong dose response relationship was noted with higher neurotoxicity was caused being noted in patients having higher doses. In the Kurtzberg study, age, prior high dose cytosine arabinoside, prior vincristine and leukemic cells in the CSF, and prior CNS disease increased toxicities.⁸ Nelarabine has now been approved for the management of adults and pediatric patients with T-cell ALL or T-cell lymphoblastic lymphoma with refractory disease with at least two previous chemotherapy regimens.

Conclusions

Nelarabine is administered as a prodrug of ara-G which is converted to the triphosphate form incorporated into DNA which results in chain termination. There is evidence of a relationship



between ara-GTP levels response. Purine analogs such as fludarabine appear to increase the formation of the triphosphate. Future studies will emphasize efforts to develop different schedules which minimize the likelihood of having dose-limiting neurotoxicity. Apart from neurotoxicity the drug is very well tolerated.

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