Drugs 2008; 68 (4): 439-447
0012-6667/08/0004-0439/$53.45/0

Nelarabine

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Contents

Abstract

▲ Nelarabine is an anticancer prodrug of arabinofuranosylguanine (ara-G), which is metabolized in cells to the cytotoxic metabolite ara-G triphosphate (ara-GTP).

▲ Ara-GTP competes with deoxyguanosine triphosphate for incorporation into DNA. Once incorporated, it inhibits DNA synthesis and leads to high molecular weight DNA fragmentation and cell death.

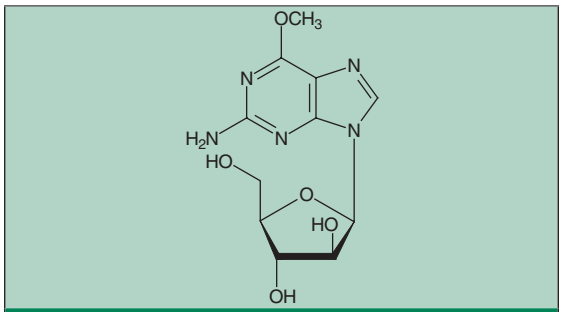
▲ In paediatric and adult patients with T-cell acute lymphoblastic leukaemia or T-cell lymphoblastic lymphoma, nelarabine induced a complete response, with or without complete haematological recovery, in approximately one-fifth of patients who had not responded to, or had relapsed following treatment with, two or more prior chemotherapy regimens.

▲ The median overall survival time was 13.1 and 20.6 weeks in paediatric and adult patients, with corresponding 1-year survival rates of 14% and 29%.

▲ Treatment-emergent adverse events were common, but non-haematological events were mostly of mild or moderate severity.

▲ Neurological events, which may be severe and irreversible, were the most likely adverse events to limit treatment.

Features and properties of intravenous nelarabine (GW506U78; 506U78; Arranon®; Atriance®)	
Approved indication	
T-cell acute lymphoblastic leukaemia or T-cell lymphoblastic lymphoma that has not responded to, or has relapsed following treatment with, two or more prior chemotherapy regimens	
Mechanism of action	
Prodrug of arabinofuranosylguanine (ara-G); inhibits DNA synthesis resulting in cell death	
Dosage and administration (cycle length 21 days)	
Paediatric patients	650 mg/m^2/day infused over 1 h for 5 consecutive days
Adult patients	1500 mg/m^2/day infused over 2 h on days 1, 3 and 5
Pharmacokinetic profile (mean values in adults after a single 1500 mg/m^2 intravenous dose given over 2 h)	
Peak plasma concentration (μmol/L)	Nelarabine: 13.9 Ara-G: 115
Area under the plasma concentration-time curve from time zero to infinity (μmol • h/L)	Nelarabine: 13.5 Ara-G: 571
Plasma elimination half-life (min)	Nelarabine: ≈30 Ara-G: ≈180
Most common treatment-emergent neurological adverse events in clinical trials	
Paediatric patients (affecting >5%)	Headache, peripheral neuropathy, somnolence, hypoaesthesia, seizures
Adult patients (affecting >15%)	Somnolence, dizziness, peripheral neuropathy, hypoaesthesia



Nelarabine

Acute leukaemias are a heterogeneous group of disorders that can be broadly grouped according to abnormal blast cell lineage into T- or B-cell acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemia.[1] Lymphoblastic lymphoma (LBL) is classified as a non-Hodgkins lymphoma, but can also be considered a variant of acute lymphoblastic leukaemia.[2] T-cell lineage malignancies are rare. T-cell ALL (T-ALL) makes up about 15–20% of child and 25% of adult ALL, which has an incidence of 1–1.5 per 100 000 population.[2,3] T-cell LBL (T-LBL) is diagnosed in 80% of patients with LBL, but these account for <2% of all non-Hodgkin's lymphoma, which affects ≈17 persons per 100 000 population.[4,5]

Advances in the treatment of acute leukaemias and lymphomas have led to markedly improved survival, especially in younger patients.[6] For instance, pooled data from five trials indicate that in patients aged <30 years with ALL the complete response (CR) rate after initial induction therapy was 90%, with an overall survival rate of 58% at 3 years.[6] However, patients with T-cell leukaemias have lower response rates than those with B-cell leukaemias and, for those who do not respond to initial chemotherapy induction regimens, the outcome is especially poor.[7] Generally, these patients are refractory to further chemotherapy regimens or relapse quickly after second remission induction, and the disease is then rapidly progressive.[7,8] Irrespective of the particular leukaemia subtype, salvage therapies in relapsed patients lead to an overall survival at 5 years as low as 7%.[9] For a small number of patients, stem-cell transplantation (SCT) may lead to prolonged survival, with complete remission being a prerequisiste for successful SCT.[10]

The need for new chemotherapy regimens for the treatment of refractory leukaemia has led to the investigation of nucleoside analogues. These agents, which include both purine and pyrimidine analogues, have widely different chemical properties and cytotoxic mechanisms of action, although all compete with naturally occurring nucleosides in DNA or RNA synthesis and/or act as inhibitors of cell enzymes essential for synthesis of these nucleic acids.[11] Although there is evidence that the deoxyguanosine analogue arabinofuranosylguanine (ara-G) is toxic to T-cells and might be beneficial in the treatment of T-cell malignancies, it has not undergone clinical evaluation because of its low water solubility.[12-14] Nelarabine (Arranon®, Atriance®)[1] was developed as a clinically useful water soluble prodrug of ara-G.

Intravenous nelarabine has recently been approved in the EU and US for the treatment of paediatric and adult patients with T-ALL or T-LBL whose disease has not responded to, or has relapsed following treatment with, two or more prior chemotherapy regimens. This review focuses on the pharmacological characteristics of intravenous nelarabine and its clinical use in the approved indications. An in-depth discussion of the efficacy of nelarabine in other populations, including patients with refractory T-ALL or T-LBL whose disease has not responded to one prior chemotherapy regimen, is beyond the scope of this review.

1. Pharmacodynamic Profile

This section provides a brief overview of the key pharmacodynamic properties of nelarabine relevant to its use in patients with T-ALL or T-LBL based on data from *in vitro* studies and phase I and II clinical trials,[13,15-17] recent reviews,[14,18,19] the manufactur-

1 The use of trade names is for identification purposes only and does not imply endorsement.

er's prescribing information[20,21] and the European Medicines Agency (EMEA) scientific discussion.[2]

- Nelarabine is rapidly metabolized to ara-G, which, in turn, is phosphorylated to ara-G triphosphate (ara-GTP) [section 2], which appears to have the main cytotoxic effect in T-cell malignancies.[14,15] There are higher ara-GTP concentrations in responders than non-responders suggesting that response to treatment in an individual patient may be determined in part by factors that affect ara-G phosphorylation to ara-GMP and subsequently to ara-GTP in that patient.[16-18]

- The chief mechanism of action of ara-GTP in T-lymphoblastoid cells is through competition with deoxyguanosine triphosphate for incorporation into DNA.[14] Ara-GTP is a 'false nucleotide' and, as such, it prevents DNA replication by resisting further deoxynucleotide additions leading to inhibition of DNA synthesis, high molecular weight DNA fragmentation and cell death.[14]

- Ara-GTP, like other nucleoside analogues, reaches concentrations in immature T-cell lines that are 20- to 40-fold higher than in B cells[2] and is more likely to produce cell death in T cells.[13,18] Higher ara-GTP concentrations are likely a determinant of T-cell selective toxicity, but other factors are also at play, possibly resistance of non-T cells to ara-G and induction in T cells, but not B cells, of an apoptosis stimulation factor-mediated pathway that leads to cell death in bystander cells.[13,18]

- In human T-cell lines, the cytotoxicity of nelarabine was similar to that of ara-G (concentrations that produced 50% inhibition were 0.31–4.4 and 0.31–5.0 μM) and 20-fold greater than in B cells.[2]

- The clinical response to nelarabine treatment may be linked to the extent of cellular accumulation of ara-GTP.[16-18] In a phase I clinical trial of patients with a wide spectrum of haematological malignancies (n = 26), T lymphoblasts accumulated more ara-GTP than cells of other haematological malignancies and normal mononuclear cells ($p = 0.0008$), and levels were higher in clinical responders than non-responders (median 157 vs 44 μmol/L; $p = 0.0005$).[16]

- Similarly, in a phase II trial of patients with acute and indolent leukaemias (n = 13), the median peak intracellular level of ara-GTP was 30-fold greater in leukaemic cells of seven patients achieving CR, partial or haematological responses than in patients who did not respond (890 vs 30 μmol/L; $p = 0.001$).[17]

- Nelarabine's cytotoxic and immune system modulatory effects are not restricted to T-leukaemic cells, but also affect bone marrow and other tissues[20] and are likely to be associated with the clinical toxicity observed with nelarabine (section 4), although other mechanisms may also be involved.[19]

2. Pharmacokinetic Profile

The pharmacokinetic data for intravenous nelarabine discussed in this section are from phase I and II trials in adults and in children/young adults aged <21 years with treatment refractory T-ALL and T-LBL summarized in the manufacturer's prescribing information.[21] Data are also available from recent reviews of nelarabine.[14,22]

- Following intravenous administration, nelarabine is rapidly metabolized by *O*-demethylation to ara-G by adenosine deaminase, which is abundant in red blood cells and large body organs.[14,22] The pharmacokinetics of multiple doses of nelarabine were predictable after a single dose.[21]

- As a result of rapid metabolism, nelarabine is soon undetectable in the blood and there is a much greater exposure of tissues to ara-G than to nelarabine.[14,22] In adults, following a 1500 mg/m^2 intravenous infusion of nelarabine over 2 hours, mean peak plasma concentrations for nelarabine and ara-G were 13.9 and 115 μmol/L, and corresponding values for the mean area under the plasma concentration-time curve from time zero to infinity were 13.5 and 571 μmol • h/L.[21]

- A further effect of rapid conversion to ara-G is that the plasma elimination half-life ($t_{1/2}$) of nelarabine is short compared with that of ara-G (30 minutes vs 3 hours).[21]

- Ara-G is transported into lymphoblasts where it is phosphorylated, chiefly by deoxycytidine kinase

and deoxyguanosine kinase, to the cytoplasmic metabolite ara-GTP.[2] Intracellular ara-GTP is retained for an extended period, and as a result, its $t_{1/2}$ could not be determined.[21] However, its apparent extended availability ($t_{1/2}$ >24 hours) is consistent with using an alternate-day administration strategy as used in adult, but not paediatric, patients.[22]

- Both nelarabine and ara-G are widely distributed throughout the body, with the highest radioactivity levels after a single infusion of ^{14}C-nelarabine detected in kidney, gall bladder, liver and spleen, and lower levels detected in the CNS.[2] *In vitro* studies show that neither nelarabine nor ara-G are substantially bound to plasma proteins (<25%) and that binding is independent of plasma concentrations up to 600 μM.[21]
- Although nelarabine is mainly metabolized to ara-G, which is then hydrolyzed to guanine, a portion of nelarabine undergoes hydrolysis to methylguanine, which is metabolized to guanine through *O*-demethylation. In turn, guanine is metabolized to xanthine and uric acid.[21]
- In adult patients, small quantities of nelarabine and ara-G are eliminated by the kidneys.[21] After a single intravenous infusion of nelarabine, the mean proportions of the administered dose excreted in the urine as unchanged nelarabine and as ara-G were 5.3% and 23.2%.[21] The corresponding values for mean renal clearance were 9.0 and 2.6 L/h/m^2.[21]
- Generally, phase I trials showed no significant differences in the pharmacokinetics of nelarabine between paediatric and adult patients or between males and females.[14] Pooled data from phase I trials in patients receiving doses of 104–2900 mg/m^2 showed that the mean clearance of nelarabine on day 1 of treatment was 138 and 125 L/h/m^2 in adult and paediatric patients. Clearance of ara-G was 9.5 L/h/m^2 in adults and 10.8 L/h/m^2 in paediatric patients.[21]
- Clearance of ara-G was reduced in adult patients with mildly or moderately impaired renal function.[21] Compared with patients with normal renal function, clearance was 7% lower in patients with mild renal impairment (creatinine clearance [Cl_{CR}] = 50–80 mL/min).[21] Close monitoring for toxicity is recommended in patients with renal impairment (Cl_{CR} <50 mL/min).[21] In the absence of data in patients with moderate to severe impairment of renal function, no dosage recommendations are provided for this patient population.[21]
- In *in vitro* studies, nelarabine or ara-G had no significant effects on hepatic cytochrome P450 (CYP) isoenzymes 1A2, 2A6, 2B6, 2C9, 2C19, 2D6 or 3A4, indicating that nelarabine is unlikely to have clinically important interactions with drugs metabolized by these CYP isoenzymes.[21]
- It is recommended that nelarabine not be used in combination with adenosine deaminase inhibitors, such as pentostatin, as these could reduce conversion of nelarabine to ara-G, thereby reducing its efficacy.[21]

3. Therapeutic Efficacy

The efficacy of intravenous nelarabine in patients with refractory or relapsed T-ALL or T-LBL was evaluated in phase II, noncomparative, open-label, multicentre trials in children and young adults aged <21 years when first diagnosed (Children's Oncology Group trial; hereafter referred to as the paediatric trial)[23] and adolescents and adults aged ≥16 years (Cancer and Leukaemia Group B trial 19801; hereafter referred to as the adult trial),[7] and in the GMALL (German Multicentre Study Group for Adult ALL) trial in adults aged ≥19 years (reported as an abstract and discussed separately).[24]

Although these trials also included patients with relapsed or refractory disease who had received only one prior chemotherapy regimen, this section focuses chiefly on data for the approved indication of patients whose disease had not responded to, or had relapsed following treatment with, at least two chemotherapy regimens. The data presented here are derived from the US FDA[25] and EMEA[2] scientific reviews of nelarabine, as these data are the most complete for patients with the approved indication.

The paediatric[23] and adult[7] trials recruited 153 and 40 patients; of these, 39[2,23,25] and 28[7] had not responded to, or had relapsed following treatment with, at least two prior chemotherapy regimens. The median patient age was 11 years (range

0.6–21.7 years)[23] and 34 years (range 16–66 years).[7] In the paediatric trial, patients were included in the approved indication group if they had ≥25% bone marrow blasts whether or not they also had extramedullary relapse, but were excluded from the group if they had CNS relapse.[23] In the adult trial, relapsed or refractory disease was defined as the presence of >10% lymphoblasts in the bone marrow or >1000 lymphoblasts/μL in the blood after achieving a treatment response, and patients were required to express two or more cell surface antigens (surface or cytoplasmic CD1a, CD2, CD3 or surface CD4, CD5, CD7 or CD8). Patients with >25% lymphoblasts in the bone marrow were classified as having T-ALL rather than T-LBL.[7]

Exclusion criteria in the paediatric trial included isolated CNS relapse, severe uncontrolled infection, predicted life expectancy <8 weeks, Karnovsky performance status ≤50%, abnormal hepatic or renal function, current anti-cancer therapy, treatment in the prior 6 weeks with nitrosourea compounds or craniospinal or hemipelvic radiotherapy, persistent grade 2 neurotoxicity, or lack of recovery from neurotoxicity resulting from prior therapy.[23] In the adult trial, exclusion criteria included leukaemic cells positive for myeloperoxidase or Sudan Black stains, myeloid markers CD33 and/or CD13 if the only T-cell markers were CD4 and CD7, seizure disorder, neurological toxicity ≥grade 3 in prior treatments, any preexisting neuropathy ≥grade 2, CNS leukaemia or lymphoma requiring intrathecal radiation, or impaired creatinine clearance within 48 hours of treatment.[7]

The nelarabine dosage was adjusted downward as a result of observed neurological adverse events.[7,23] In the initial group of paediatric patients, nelarabine 1.2 g/m^2/day was infused over 1 hour for 5 consecutive days every 3 weeks, but was reduced to 650 mg/m^2/day for 5 days in subsequent patients (data are included only for patients receiving the lower dosage).[23] In patients free of CNS leukaemia, triple intrathecal therapy (methotrexate, cytarabine and hydrocortisone) was then given at the treating clinician's discretion after the first two nelarabine treatment cycles.[23]

In adult patients, the treatment regimen for the first three patients was nelarabine 2200 mg/m^2/day infused over 2 hours on days 1, 3 and 5, but for subsequent patients, the dose was reduced to 1500 mg/m^2 (data reported for both doses).[7] This sequence was repeated if bone marrow biopsies on day 22 (repeated at day 29 if hypocellular) showed residual or recurrent leukaemia. In patients with a CR, two further cycles of nelarabine were given (on days 1, 3 and 5 every 21 days) as a consolidation therapy.[7]

In the paediatric trial, CR was defined as <5% blast cells in a bone marrow sample with adequate bone marrow cellularity (taken on day 21 of the first cycle), and in patients with extramedullary disease, no radiological evidence of disease.[23] CR was confirmed by a second assessment ≥3 weeks later (day 21 of the second cycle). In the adult trial, CR in patients with T-ALL was defined as absolute neutrophil count >1500/μL, platelets >100 000/μL, no circulating blasts, bone marrow with trilineage haematopoiesis and cellularity >20%, <5% blasts in bone marrow (none with neoplastic appearance) and absence of all extramedullary signs of disease, while CR in patients with T-LBL was defined as the absence of all measurable disease and no biochemical changes related to the disease.[7] A response was only considered valid if maintained for ≥1 month. In both trials, CR-incomplete (CRi) was defined as CR without full haematological recovery.[2,7,25]

Other endpoints included duration of response with or without further anti-cancer treatment (from response assessment to relapse, death or last contact), overall survival (from treatment initiation to death) and, retrospectively, the proportion of patients undergoing SCT after nelarabine treatment.[2,25]

Selected data are also presented from the GMALL trial, which included patients with refractory T-ALL or T-LBL, most of whom were within the approved indication.[24] Forty-six patients had T-ALL and 4 had T-LBL, with 43 patients presenting

with bone marrow disease and 7 with only extramedullary involvement. Of 49 evaluable patients, 34 were in first relapse (of these, 32 were refractory to at least one salvage chemotherapy regimen), 7 were in second relapse, 7 were in second relapse after SCT and 2 patients never reached a CR. Patients received nelarabine 1500 mg/m^2/day on days 1, 3 and 5 (number of cycles not stated).[24]

- Nelarabine treatment induced CR or CRi in approximately one-fifth of paediatric and adult patients who had not responded to, or had relapsed following treatment with, two or more prior chemotherapy regimens[2,25] (figure 1).
- The CR rate in paediatric patients was 13% (95% CI 4, 27) and a further 10% had a CRi, for a total CR/CRi response rate of 23% (95% CI 11, 39).[2]
- In the adult trial, 18% had a CR (95% CI 8, 34) and a further 3% had a CRi, for a total CR/CRi response rate of 21% (95% CI 8, 41).[2]
- The duration of response was protracted for individual patients, especially among adult responders (two of six adult patients with CR/CRi had a response continuing beyond 150 weeks).[2] For responders as a group, the duration of CR ranged from 4.7 to 36.4 weeks in paediatric patients (median 12.3 weeks) and from 15.1 through >195.4 weeks in adult patients.[2]
- In paediatric patients, irrespective of whether or not they responded to nelarabine, the median overall survival time was 13.1 weeks (95% CI 8.7, 17.4), with a 1-year survival rate of 14% (95% CI 3, 26).[2]
- In adult patients, the median overall survival time was 20.6 weeks (95% CI 10.4, 36.4), with a 1-year survival rate of 29% (95% CI 12, 45).[2]
- A small number of patients who reached a CR/CRi received SCT (four of nine paediatric and one of six adult patients).[25]
- In the GMALL trial, 25 patients (51%) achieved a CR (specific response criteria are not available) and 19 patients went on to receive SCT (median time to SCT 41 days).[24]
- Patients whose disease had not responded to, or had relapsed following treatment with, just one prior chemotherapy regimen had better outcomes than those described here, although this was more marked for paediatric than adult patients.[2] For instance, 42% (95% CI 25, 61) of paediatric and 18% (95% CI 2, 52) of adult patients had a CR (corresponding CR/CRi rates were 48% and 27%), and the 1-year survival rate was 33% in paediatric and 36% in adult patients.[2]

4. Tolerability

This section provides an overview of the tolerability profile of intravenous nelarabine in the phase II trials discussed in section 3. Descriptive data presented are for the total trial populations of paediatric (n = 84) or adult (n = 38) patients with T-ALL or T-LBL whose disease had not responded to one or more prior chemotherapy regimens and who were treated with recommended dosages of nelarabine.[7,23] Pooled data for 103 patients receiving nelarabine in the adult trial[7] or a trial in adult patients with chronic lymphocytic leukaemia (not discussed elsewhere in this review) are also presented.[20] Toxicity was graded according to US National Cancer Institute Common Toxicity Criteria.[26]

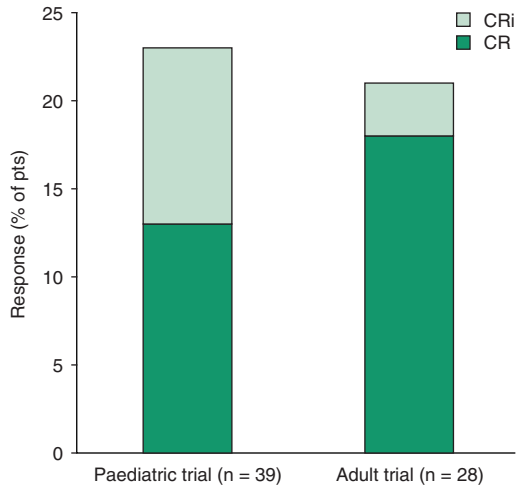


Fig. 1. Efficacy of intravenous nelarabine in patients (pts) with refractory or relapsed acute T-cell lymphoblastic leukaemia or T-cell lymphoblastic lymphoma. Complete response (CR) and incomplete response (CRi) rates from phase II, noncomparative, open-label, multicentre trials are shown.[2,25] Pts received 21-day cycles of nelarabine 650 mg/m^2/day infused over 1 hour for 5 days (paediatric trial)[23] or 1500 mg/m^2/day over 2 hours on days 1, 3 and 5 (adult trial).[7]

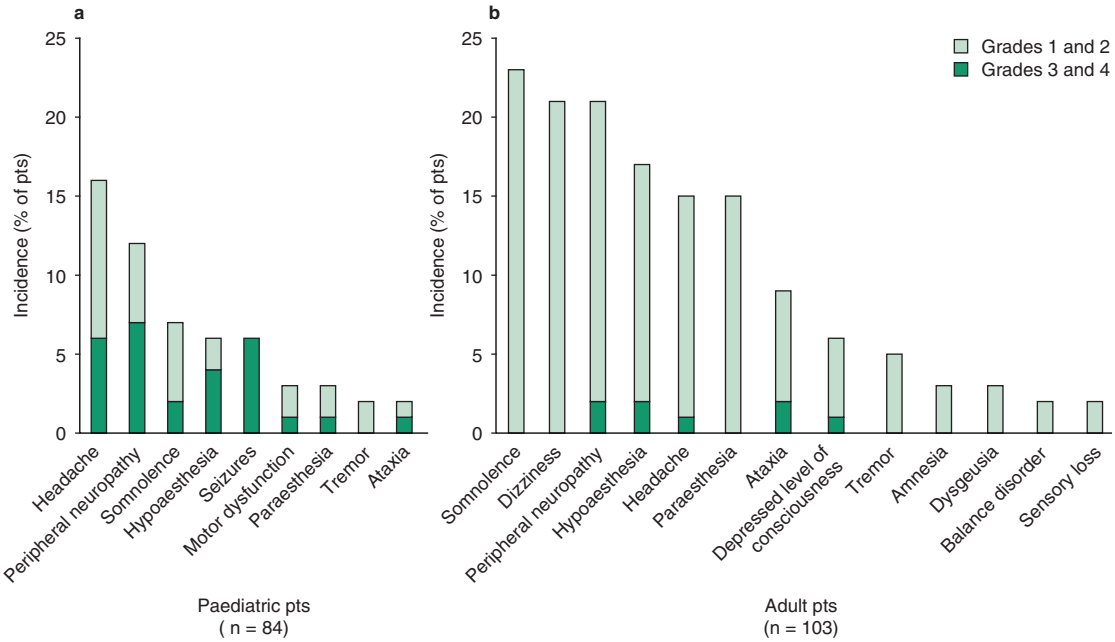


Fig. 2. Neurological treatment-emergent adverse events in paediatric and adult patients (pts) undergoing treatment with intravenous nelarabine.[20] Incidence of neurological adverse events occurring with a frequency of ≥2% in (**a**) paediatric pts aged ≤21 years with T-cell acute lymphoblastic leukaemia (T-ALL) or T-cell lymphoblastic lymphoma (T-LBL) receiving 21-day cycles of intravenous nelarabine 650 mg/m^2/day on 5 consecutive days[20] and (**b**) a pooled analysis[20] of data from adult pts aged ≥16 years with T-ALL, T-LBL[7] or chronic lymphocytic leukaemia[20] receiving 21-day cycles of intravenous nelarabine 1500 mg/m^2/day on days 1, 3 and 5.

- As might be expected in treated leukaemic patients, treatment-emergent haematological events affected ≈100% of patients.[21] In the paediatric trial, two patients did not receive all nelarabine doses in the first cycle, in neither case was this attributable to haematological toxicity.[23] In 29 patients with extramedullary relapse and <25% blasts in the bone marrow, 4 developed grade 4 haematological toxicity.[23] In the adult trial, 3 of 38 patients withdrew because of toxicity, but no withdrawals were attributed to haematological toxicity.[7]

- Neurological adverse events are the most likely adverse events to limit treatment with nelarabine (see figure 2 for neurological events reported in ≥2% of paediatric and adult patients in the phase II clinical trials).[20]

- In the paediatric trial, seizures occurred in four patients, in the context of either electrolyte disturbance or progressive CNS leukaemia.[23] Another patient, treated with anticonvulsants, continued nelarabine treatment, while one with a history of a prior seizure died during *status epilepticus* thought to be related to nelarabine treatment.

- One paediatric patient receiving a 900 mg/m^2 dose developed grade 4 peripheral neuropathy and a Guillain-Barré-like syndrome and died when withdrawn from mechanical ventilation. Two further patients experienced third and sixth cranial nerve paralyses (grade 4).[23]

- In the adult trial,[7] two patients withdrew because of peripheral sensory neuropathy (grade 2) and eight patients developed a peripheral motor neuropathy (one at grade 3). Another patient developed a lowered level of consciousness (grade 4), which resolved. One patient died as a result of cerebral haemorrhage, coma and leukoencephalopathy,[20] which was thought by the trial investigators to be unrelated to treatment with nelarabine.[7]

- In paediatric patients, the most common (affecting 10–12% of patients) non-haematological, non-

neurological, treatment-emergent adverse events were increased blood transaminases, decreased blood potassium and albumin, increased blood bilirubin, and vomiting.[20] Less common adverse events, but with a frequency of grade 3 and 4 events ≥2%, were decreased blood glucose, calcium or magnesium, and infection.[20]

- In adults, the most common (affecting 15–50% of patients) general treatment-emergent adverse events were fatigue, nausea, cough, pyrexia, diarrhoea, vomiting, constipation, dyspnoea, asthenia and peripheral oedema.[20] Other adverse events occurring less commonly, but with a frequency of grade 3 or 4 events ≥2%, were pleural effusion, pneumonia, muscular weakness, pain, dehydration, infection, increased blood AST, confusional state, petechiae and hypotension.[20]

5. Dosage and Administration

In patients with T-ALL or T-LBL whose disease has not responded to or relapsed following treatment with two or more chemotherapy regimens, the recommended paediatric dosage is 650 mg/m^2/day infused intravenously undiluted over 1 hour for 5 consecutive days, repeated every 21 days.[20,21] The recommended adult dosage is 1500 mg/m^2/day infused undiluted over 2 hours on days 1, 3 and 5, and repeated every 21 days.[20,21] In the EU, for patients aged 16–21 years, the prescribing physician should consider which of the two possible treatment regimens is appropriate.[21] As yet, the recommended duration of treatment has not been established.[20] In clinical trials, dosages were repeated until there was evidence of disease progression, the patient no longer benefited from treatment, experienced unacceptable toxicity or became a candidate for SCT.[20]

The US and EU manufacturer's prescribing information contains a black box warning that nelarabine has been associated with severe neurological events and that cessation of nelarabine treatment is not always associated with recovery from these events.[20,21] It is strongly recommended that patients be monitored closely for neurological adverse events and that nelarabine treatment is discontinued at the first sign of grade 2 or greater neurological events.[20,21] Local prescribing information should be consulted for detailed information including contraindications, precautions and use in special populations.

6. Nelarabine: Current Status

Nelarabine is approved in the US and EU for the treatment of paediatric and adult patients with T-ALL or T-LBL whose disease has not responded to, or has relapsed after treatment with, at least two prior chemotherapy regimens.[20,21] In noncomparative phase II trials, nelarabine induced CR with or without a full haematological response in approximately one-fifth of paediatric and adult patients with this clinically challenging indication. The toxicity of nelarabine is generally acceptable, but serious treatment-limiting neurological adverse events may occur in some patients. The efficacy of nelarabine in combination chemotherapy for newly diagnosed T-ALL is currently being investigated in a large, multinational, phase III trial in patients aged 1–30 years.[27]

Acknowledgments and Disclosures

The manuscript was reviewed by: **J. Kline**, Department of Medicine and Cancer Research Centre, University of Chicago, Chicago, Illinois, USA; **D. Marks**, Department of Adult Bone Marrow Transplantation, Bristol Royal Hospital for Children, Bristol, UK; **C. Tam**, Department of Leukemia and Stem Cell Transplantation, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA.

The preparation of this review was not supported by any external funding. During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on this article; changes based on any comments received were made on the basis of scientific and editorial merit.

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