1 h. Evaluation of the response on day 21 and 49 included chest X-ray, computerised tomography for abdominal masses, and ultrasound for liver metastases [6] or peripheral lymph nodes. Toxicity was given WHO grading. On day 49, patients with non-progressive disease received fotemustine (100 mg/m^2 maintenance) given every three weeks until disease progressed or cumulative toxicity developed.

Of the 16 patients who entered the study, 2 were not evaluable; 1 because of hepatic dysfunction at entry, the other because of non-compliance during the induction cycle. 10 patients were male and 4 female; median age was 54 (range 45–76) years and median Karnofsky score was 80% (range 50–100). The metastatic sites were: liver (5), liver and other sites (4), lung (3) and lymph nodes (2). The overall response rate was 1 of 14. 1 patient with metastatic subclavicular lymph nodes had a partial response for 1 year; another had a minor response in hepatic lesions for 9 months. 2 patients were stabilised for 4 months, and 10 patients had progressive disease (1 had a partial response in a cutaneous site).

Toxicity was mainly haematological. The median value of the nadir for leucocytes and thrombocytes was 1.5 (0.8 to greater than 4) $\times$ 10^9/l and 30 (12 to greater than 100) $\times$ 10^9/l, respectively. Grade 4 thrombocytopenia occurred in 6 of 13 patients but none required platelet transfusion. The median nadir for thrombocytopenia was on day 35 and for leucopenia on day 49. Recovery was achieved within 8 days. The high toxicity against platelets was surprising. In comparison with previously reported results, the only difference in our study, apart from a small sample which may cause statistical insignificance, was tumour type. Reports on activity and toxicity of fotemustine in different tumour types show substantial variability in haematotoxicity: less than 10% grade 4 leucopenia and thrombocytopenia in malignant melanoma and primitive brain tumours; and 20% leucopenia and 30% thrombocytopenia grade 4 in non-small cell lung carcinoma, suggesting different susceptibility according to histological type [4, 5, 7, 8].

No delay was observed during induction and no dose reduction made during induction or maintenance therapy. Of the 5 patients given maintenance treatment, 3 had a 1–3 week delay because of prolonged neutropenia, and 1 had to wait 3 months because of prolonged hyperbilirubinaemia. Hepatic toxicity with a transient increase in transaminases (WHO grade 2) was observed in 3 patients, and in 1 patient it was accompanied by an increase in alkaline phosphatase (grade 2) for 1 month and hyperbilirubinaemia (grade 4) for 3 months. This jaundice episode was documented by a transcutaneous liver biopsy showing chemical hepatitis. As the patient had a minor response of liver metastases, he received one administration of fotemustine as first maintenance treatment, with no major adverse effect; however, treatment was discontinued because of further progressive disease. Nausea and vomiting were moderate, 30% of drug administrations giving a toxicity grade 2 or 3, with prophylactic doses of antiemetics.

With 1 response out of 14 patients, our results are similar to the previously reported activity of nitrosoureas in advanced colorectal cancers [9]. With the intra-arterial hepatic route, a response rate of 20% has been observed with fotemustine alone for liver metastases of colorectal origin [10]. Haematological toxicity may be severe, but digestive tolerance, compared with other nitrosoureas, is higher and mutagenicity in experimental models is lower [11]. These data and the possibility to overcome the mechanisms of resistance to nitrosoureas justify further investigation of fotemustine in colorectal cancer.

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Adult T-cell Leukaemia/Lymphoma and Horizontally Transmitted Human T-lymphotropic Virus Type I

Shinkan Tokudome

HUMAN T-LYMPHOTROPIC virus type I (HTLV-I) carriers vertically infected from their mothers are at risk of adult T-cell leukaemia/lymphoma (ATL) [1]. However, it is not known whether virus carriers horizontally infected through sexual contacts or through transfusion are similarly at risk [2].

If female HTLV-I carriers infected by sexual transmission from male partners are at risk of ATL, discrepancies by gender will exist in the age at onset, age distribution and other related epidemiological variables. However, the mean age at onset of ATL among females is greater than that of males, but statistically insignificant [3]. Two density function variables, according to the Weibull distribution, among females were almost identical to those of males, which suggests no difference, by gender, in leukemogenesis [4]. Moreover, the latency period from infection

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with HTLV-I to onset of ATL is very long in both sexes. If the latency period is equal to the mean age at onset of ATL, the mean life expectancy in females of 80.5 years in Japan in 1985 [5] is much smaller than the age (30 years or more) at which a rising number of female HTLV-I carriers, due to seroconversion via sexual transmission, occurs plus the mean age at onset (55.8 years) [4] of ATL among females. No bimodal age distribution for onset of ATL among females was reported. Therefore, the number of ATL cases among female HTLV-I carriers sexually infected from male partners is small, if any.

The risk of ATL among HTLV-I carriers horizontally infected via transfusion, irrespective of gender, is not known. A blood bank system has only been in operation in Japan for about 40 years. If the latency period is unrelated to infection route, onset of ATL among virus carriers infected via transfusion would not have occurred.

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Toxic Epidermal Necrolysis during Chlorambucil Therapy in Chronic Lymphocytic Leukaemia

C. Barone, A. Cassano and A. Astone

WE REPORT a 57-year-old female with chronic lymphocytic leukaemia who had toxic epidermal necrolysis (TEN) after chlorambucil alone (0.1 mg/kg per day). During initial treatment a confluent maculopapular erythema of trunk, legs, feet and mucous membranes erupted followed by large flaccid blisters and fever. Despite administration of 6-methylprednisolone the rash became widespread and exfoliation occurred. After 18 days of chlorambucil therapy, white blood cell (WBC) count was 21 $\times$ 10^9/l and gram-negative sepsis had developed; therefore chlorambucil was discontinued. Erythromycin and gentamicin were started and the eruption and sepsis resolved after 8 days. The patient was discharged without further treatment (WBC 5 $\times$ 10^9/l).

4 months later, the patient's WBC rose to 30 $\times$ 10^9/l and chlorambucil alone was restarted. No other drugs (particularly allopurinol) were used to minimise the risk of cutaneous reaction. A few hours after chlorambucil (2.5 mg) was taken, the patient had a diffuse erythema of the skin with eruption of flaccid blisters on buttocks and thighs. During the following days large sheets of necrotic superficial epidermis detached from the skin. A cutaneous biopsy showed coagulative necrosis of keratinocytes, dermoepidermal separation and perivascular lymphocytic infiltration. Marked sensitivity to chlorambucil caused TEN. Prompt therapy with prednisone resolved the toxic reaction.

2 months after this episode, the patient had a skin-patch test. Chlorambucil in vaseline (5 and 10%) was applied on the intact skin of the forearm (Dermo-test Diagent). A papular vesicular eruption occurred after 48 h with a maximum at 72 h. Patch tests performed with European Standard Series were negative. 10 volunteers, 5 previously treated with chlorambucil, had the same test without developing a reaction.

Chlorambucil has been associated with a cutaneous reaction in only a few cases [1–4], and our report of TEN is rare. The pathogenesis of TEN is unclear: besides immunological causes, cytochemical and photosensitivity mechanisms seem to play a role.

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Neoadjuvant Low-dose Chemotherapy with Insulin in Breast Carcinomas

Steven G. Ayre, Donato Perez Garcia y Bellon and Donato Perez Garcia Jr

WE HAVE developed a neoadjuvant chemohormonal therapy for breast carcinomas without surgery or radiotherapy. Cyclophosphamide, methotrexate and 5-fluorouracil are administered, with insulin as a biological response modifier to potentiate anticancer drug effects [1]. This regimen affords maximum breast conservation and minimum patient discomfort.

Breast malignancies are histologically verified by fine needle biopsy. Insulin/chemotherapy cycles are repeated twice a week for 3 weeks, and then weekly for another 3–6 weeks depending on clinical findings. Fasting subjects receive insulin (0.3 U/kg) and, at onset of hypoglycaemia, cyclophosphamide 8 mg/m^2,

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