kaemic cells, a typical phenotype of ATL as reported previously [2], was observed in addition to the existence of $CD38^+$ PCA-1 positive plasma cells which coexpressed cytoplasmic immunoglobin (Ig) G, λ.

Monoclonal increment of Ig G, λ (4570 mg/dl) was detected by immunoelectrophoresis. Both IgM and IgA were suppressed. Absence of NK activity as well as low number of NK cells [3] were found. Anti-HTLV-I (human T-cell leukaemia virus-I) antibody was identified by passive agglutination, immunofluorescence and enzyme-linked immunosorbent assay testing [4]. In bone marrow, numerous myeloma cells were found in addition to ATL cells, indicating the co-existence of multiple myeloma. The ATL cells showed gene rearrangement for the T-cell receptors TcRβ and TcRγ. The ATL cells overexpressed HRAS p21 and p53 suppressor oncogene products, which suggests the existence of point mutations [5], as well as *myc* and PCNA (proliferating cell nuclear antigen, p36kD). The patient died from bacterial meningitis associated with central nervous system invasion of ATL cells.

We identified ATL-derived factor (ADF) [6] in the cytoplasm of both the gastric and colon adenocarcinomas, and invading ATL cells by indirect immunofluoroscopy and immunohistochemistry [7]. We also identified *ras* p21 products in these neoplasms, using anti-p21 *ras* monoclonal antibody.

The observations in this rare case suggest a possible association between ATL cells and premalignant cells, through ADF or other unknown factors in the activation of *ras* oncogenes. Subsequent suppression of host immune defence mechanisms in ATL permits the emergence of the secondary neoplasms [8]. Recent reviews by Hunter [9] and Sawyers *et al.* [10] are consistent with this hypothesis. ATL patients and/or HTLV-1 carriers should be carefully examined for their possibility of developing malignant neoplasms. The association of point mutation on *ras* oncogene and p53 suppressor oncogene remains to be elucidated [5].

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Treatment of Advanced Neuroblastoma

A.D.J. Pearson, M.M. Reid and A.W. Craft

EVANS *et al.* [1] make some interesting comments about treatment of high-risk neuroblastoma in general and our and the Royal Marsden's papers on consolidation therapy in particular. We would like to answer these.

The main purpose was to describe toxicity, not to claim improved efficacy. We wished to highlight the fact that significant toxicity may result from the use of multiple drugs as consolidation therapy with autologous marrow rescue. From our review of the literature on consolidation therapy, we concluded that a 40% 2 year event-free survival could be achieved with multiple or single agents and could not convince ourselves that more agents resulted in better survival. In this we agree with Corbett *et al.* [2]. With this background, and despite our encouraging results, any benefit of additional chemotherapy during consolidation will be shown only by carrying out randomised studies of single- vs. multiple-agent consolidation therapy in a group who have received uniform, preconsolidation induction therapy.

There are a number of potential reasons for the discrepancy in progression-free survival rates between the two studies. We did say that there is "uncertainty about the relative contributions to survival of induction and consolidation regimens" and pointed out that our study did not attempt to address this issue. However, readers will not be misinterpreting our paper if they inferred that we suspect differences in induction therapy might be critical in influencing overall outcome. The relative importance of altering the induction schedule, in particular increasing dose intensity with the rapid schedule of chemotherapy at 10-day intervals, will be shown in the randomised European Neuroblastoma Study Group 5 study in which the two arms consist of induction therapy with the same drugs at the same dose but different dose intensity.

Any difference in survival between the two studies cannot be due to purging of the marrow by one group rather than the other. Both papers state that unpurged marrow was used. The only obvious handling difference was that we used refrigerated unmanipulated marrow whilst the Royal Marsden Group used cryopreserved marrow. If this difference in handling (rather than chance, consolidation or induction therapy) resulted in differences in survival, we need to develop a rationale for the mechanism and investigate it. We think it is an unlikely explanation.

The assessment of outcome would have been more obvious if we had not included 1 patient with stage 3 disease. We did so

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because the major objective was to report toxicity not outcome. Our present approach is to use intensive induction and consolidation therapy only for those patients with stage 4 neuroblastoma over the age of 1 year. We agree with Evans *et al.* [1] that the use of other prognostic factors, especially biological features, may allow us to define poor risk neuroblastoma more accurately.

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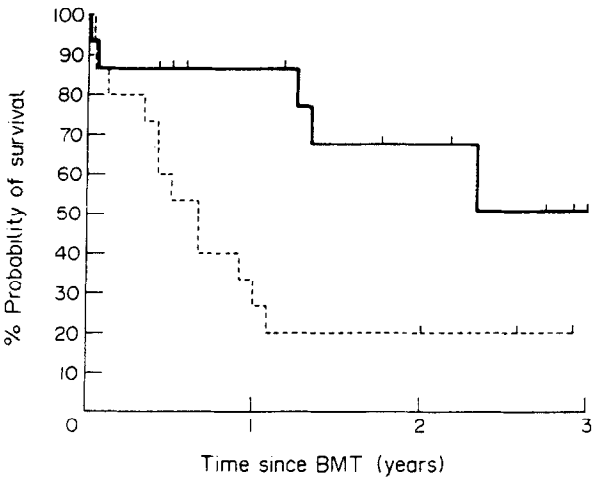

Fig. 1. Overall survival of patients treated with rapid (—) or standard (---) OPEC.

Treatment of Advanced Neuroblastoma

Robin Corbett and Ross Pinkerton

THE REVIEW by Evans *et al.* [1] considers the problems and challenges facing oncologists who treat this aggressive disease and comments specifically on two studies published independently in the same issue of the *European Journal of Cancer* reporting the use of high-dose OMEC (vincristine, melphalan, etoposide and carboplatin) as consolidation treatment in advanced neuroblastoma [1–3]. Evans *et al.* note that there is a significant difference in survival between these two studies and speculate as to the explanation for this. We agree that the differences in scheduling of OMEC (administered over 1 or 5 days) is unlikely to account for the difference. The reviewers enquire about the influence of purging the marrow, although as described in the respective texts this was not done. The criteria for entry into the studies and patient populations treated were also similar.

A possible explanation for the apparent survival difference is the scheduling of the induction regimens employed. 15 of the 16 Newcastle patients received a dose-intense, 10-day rapid scheduling of OPEC (vincristine, cisplatin, etoposide and cyclophosphamide). In contrast, 17/20 patients reported by Corbett *et al.* received standard dose intensity OPEC 3-weekly depending on count recovery. Analysis of the rapid vs. standard OPEC groups (all patients received either schedule of OMEC as consolidation treatment) showed a significant difference ($P < 0.025$) in outcome (Fig. 1, unpublished data). These data are presently being reanalysed to establish whether the significance still holds out.

We would dispute the statement by Evans *et al.* [1] doubting "if any investigator these days would be content to use a single agent for consolidation" and would like to clarify that the reference attesting to the proven efficacy of high-dose melphalan (HDM) is not the report of a pilot study in 1982 by Pritchard *et al.* [4]. The two references clearly cited in the introduction to our article refer to the European Neuroblastoma Study Group (ENSG 1) trial which is the only prospective randomised study of consolidation treatment in neuroblastoma and demonstrates a significantly longer progression-free survival for patients who received HDM [5, 6]. No subsequent published study with any combination chemotherapy or chemoradiotherapy regimen has been proven to have superior results.

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