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Clinical Oncology: Case Presentations from Oncology Centres. Intensive Treatment of Poor Prognosis Gastrointestinal Lymphoma

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CASE PRESENTATION

A 50-YEAR-OLD European engineer presented to his family doctor with intermittent right hypochondrial pain, diarrhoea and lethargy. These symptoms were initially managed with antacids and simple analgesics. His past history included a laparotomy 30 years ago for duodenal ulceration, followed by pyloroplasty and vagotomy 2 years later. Three years ago he had complained of right upper quadrant pain but a barium enema at that time was normal.

For 7 months his symptoms of dyspepsia persisted. He became anorexic and lost 19 kg in weight. In the final 3 months he developed drenching nocturnal sweats but no fever or pruritus. He returned to his general practitioner and on abdominal examination a right upper quadrant mass was felt.

His general practitioner referred him for upper gastrointestinal endoscopy which was normal. A barium enema showed narrowing of the hepatic flexure of the colon and was reported as a possible lymphoma. An ultrasound examination confirmed the presence of a solid mass in the upper abdomen.

He proceeded without delay to surgery. At laparotomy an advanced tumour was found at the hepatic flexure infiltrating the right mesocolon and the root of the small bowel mesentery. This was unresectable and a palliative ileo-transverse anastomosis was performed and a biopsy sample taken. The postoperative recovery was uneventful. A preliminary diagnosis of diffuse high grade non-Hodgkins' lymphoma was made and the patient was referred to the Department of Medical Oncology at the Christie Hospital.

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Clinical assessment

The patient was thin, with a Karnofsky performance score of 60. Multiple 2–3 cm fixed lymph nodes were palpable in the right supraclavicular fossa. There was no other peripheral lymphadenopathy and Waldeyer's ring was normal. The abdomen was distended with a 20 cm × 11 cm right upper quadrant mass. The liver and spleen were not palpably enlarged.

Staging investigations

At presentation he had a normochromic, normocytic anaemia with a haemoglobin of 11.0 g/dl. His platelets were 532 × 10^9/l, white blood count 6.6 × 10^9/l (neutrophils 63%, lymphocytes 26%, monocytes 3%, eosinophils 7%, basophils 1%, no abnormal cells). The erythrocyte sedimentation rate (ESR) was 18 mm/h. Serum protein electrophoresis revealed a raised α_2 globulin but immunoglobulin levels were normal. Serum vitamin B_{12} was 457 ng/l (normal range 140–640) and serum folate 4.1 μg/l (2–8). Serum electrolytes were normal but liver function was deranged: serum alkaline phosphatase 244 U/l (25–110), gamma glutamyl transferase 165 U/l (5–65) and lactate dehydrogenase 635 U/l (200–500). Renal function was normal. Bone marrow aspirate and trephine showed normal cellularity and maturation with reduced iron stores but no evidence of malignant infiltration. Examination of the cerebrospinal fluid was normal.

Diagnostic imaging included radiographs of the chest, postnasal space and computed tomography (CT) the chest and abdomen. Right paratracheal, tracheobronchial and anterior mediastinal lymphadenopathy was evident on the chest radiograph. Postnasal space radiographs were normal. CT confirmed enlargement of mediastinal, right internal mammary, bilateral supradiaphragmatic and retrocrural lymph nodes. All abdominal lymph node groups were involved with bulky para-aortic and paracaval nodes extending from the level of the pancreas to the aortic bifurcation (maximum diameter of 10 cm). A conglomerate

mass 22 cm × 9.5 cm was seen involving the caecum, and right colon to the hepatic flexure. In addition, bilateral renal hilar nodal enlargement and nodes in the mesocolon and root of the small bowel mesentery were seen. There was no definite parenchymal disease of the liver, spleen, kidneys or involvement of the lungs.

With nodal disease on both sides of the diaphragm and diffuse involvement of the gastrointestinal tract, greater than 10% loss of body weight and nocturnal sweats, the patient was considered to have stage IVb disease. In view of this, liver biopsy was not requested.

Review of the histology confirmed the diagnosis of a diffuse high grade non-Hodgkin lymphoma. Histological examination of the tumour biopsy obtained at laparotomy showed fibrous stroma heavily infiltrated by diffuse sheets of moderately cohesive large cells. These had inconspicuous cytoplasm and large nuclei with coarse chromatin and several peripheral nucleoli. There was a high mitotic rate and numerous apoptotic cells were present (Fig. 1). The tumour cells were positive immunohistochemically for the pan-B marker L26 (CD20) and negative for the T cell marker CD3. The neoplasm was classified as a diffuse centroblastic lymphoma in the Kiel classification (diffuse large cell, non-cleaved in the Working formulation).

Treatment

The patient was treated with VAPEC-B chemotherapy (Fig. 2). In this regimen, six drugs are administered using an alternating weekly schedule. Non-myelosuppressive agents alternate with myelosuppressive agents to ensure tumour control during recovery from myelodepression. Treatment was given for 11 weeks on an outpatient basis. Continuity of therapy to enhance tumour cell kill and prevent tumour regrowth during a brief period of intensive treatment are important characteristics of this regimen.

Myelodepression is a major side-effect of this treatment and carries significant morbidity. Corticosteroids, cotrimoxazole and ketoconazole are given continuously throughout treatment. This patient also received daily subcutaneous filgastrim (recombinant human granulocyte colony stimulating factor [G-CSF]; 230 μg/m²) except on days of myelosuppressive chemotherapy as part of a phase III trial to examine the ability of G-CSF to ameliorate neutropenia and its sequelae.

Within 1 month of starting chemotherapy all palpable disease had resolved and the chest X-ray had returned to normal. During induction chemotherapy the patient experienced a single episode of neutropenia with fever, requiring hospital admission for antibiotic treatment. He also developed grade I peripheral neuropathy and proximal myopathy. A re-staging CT at week 12 showed a residual para-aortic nodal mass of 2.2 cm × 1.4 cm and a conglomerate mass of 12 cm × 7 cm enveloping loops of bowel.

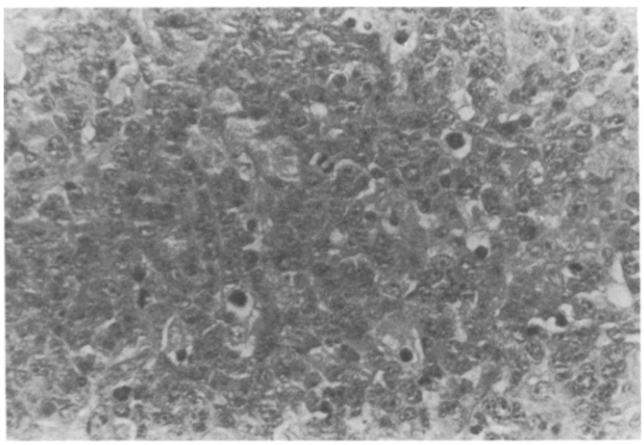

Fig. 1. Section of retroperitoneal mass showing a dense infiltrate of lymphoid cells having the morphology of centroblasts and frequent mitotic figures and apoptotic cells.

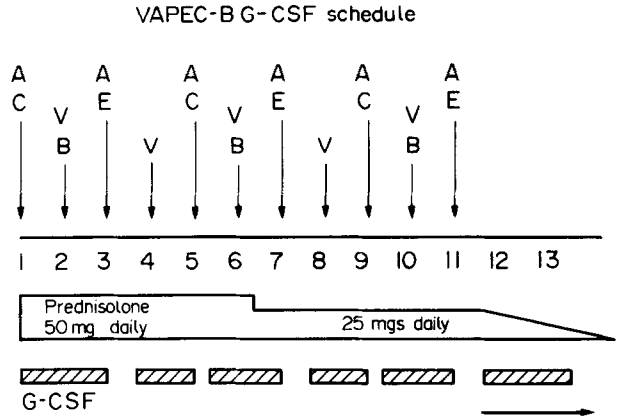

Fig. 2. VAPEC-B treatment schedule with G-CSF. The protocol covers 13 weeks. A: doxorubicin 35 mg/m² intravenously; C: cyclophosphamide 350 mg/m² intravenously; V: vincristine 1.4 mg/m² (max. 2.8) intravenously; B: bleomycin 10 mg.m² intravenously; E: etoposide 100 mg/m² postoperatively, daily × 5. Enteric coated prednisolone is given daily, 50 mg for 5 weeks, 25 mg for 5 weeks, then reducing to zero over 2 weeks. Co-trimoxazole 960 mg twice daily postoperatively and ketoconazole 200 mg eight times daily are given for 12 weeks. Shaded areas represent the time of administration of G-CSF of 230 μg/m²/day subcutaneously. G-CSF was discontinued at week 13 or when absolute neutrophil count (ANC) reached 20 × 10⁹/1, whichever was the soonest.

After achieving a partial response to induction chemotherapy, the patient entered the consolidation and ablative chemotherapy programme with autologous haemopoietic rescue. Optimising on the release of peripheral blood progenitor stem cells into the circulation following chemotherapy and G-CSF, a single leukapheresis was performed at the time of peak release of progenitors into the circulation. 1.25×10^8 mononuclear cells (MNC) per kg were collected of which 6.25×10^6 per kg were CD34-positive and 2.2×10^5 granulocyte–macrophage colony-forming units (CFU-GM) per kg. The patient proceeded to bone marrow harvest and 6.9×10^8 bone marrow cells per kg were collected.

Consolidation chemotherapy comprised three cycles of doxorubicin 50 mg/m² and cyclophosphamide 500 mg/m² at 21-day intervals. On completion, CT was normal apart from a 6.7 cm × 3.8 cm mesenteric mass. The patient was re-evaluated for ablative chemotherapy followed by haemopoietic reconstitution. The cardiac ejection fraction, creatinine clearance, thyroid function tests and clotting screen were normal. Serology for hepatitis B, cytomegalovirus (CMV) and HIV were negative.

Two weeks following completion of consolidation chemotherapy, ablative chemotherapy with busulphan and cyclophosphamide was commenced (Fig. 3) and the patient admitted to the transplant unit. 48 h after the last dose of cyclophosphamide, autologous peripheral blood progenitor cell (PBPC) alone were re-infused and G-CSF 230 μg/m²/day subcutan commenced (see Fig. 3). Intractable nausea and vomiting necessitated parenteral nutrition. He developed a fever on the third day post PBPC

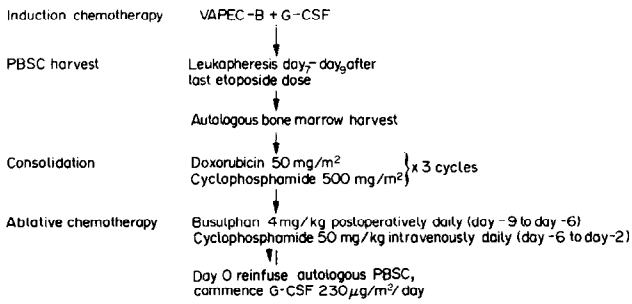

Fig. 3. Treatment schedule.

reinfusion and received 9 days of intravenous antibiotics. No organism was cultured.

Early haemopoietic reconstitution was achieved: neutrophils $> 0.5 \times 10^9/l$ and $> 1.0 \times 10^9/l$ by day 9, platelets $> 20 \times 10^9/l$ by day 13 and $> 50 \times 10^9/l$ by day 20 (Fig. 4). During his hospital stay he required 8 units of packed red cells and five platelet transfusions. He was discharged from the hospital 14 days after PBPC reinfusion. Following discharge his immediate post-transplant course was complicated by CMV infection and gastritis. No further admissions were required.

Three months after transplant, CT showed further reduction in the size of the mesenteric mass to 2.6 cm diameter. At this time abdominal radiotherapy was considered but rejected in view of his platelet count of $100 \times 10^9/l$. It is now 7 months since his transplant and the patient is working part-time and leading a full and active life. Haematological indices are all normal and there is no evidence of disease relapse.

DISCUSSION

Staging

A rapid and comprehensive assessment of disease extent is essential for the correct management of non-Hodgkin lymphoma. A detailed history should be taken and careful physical examination performed with special attention to all node-bearing areas, including Waldeyer's ring, since tonsillar disease is often associated with gastrointestinal involvement. Often, as in this case, barium contrast studies of the bowel may suggest the diagnosis and are helpful in defining the extent of disease. A full staging evaluation using techniques appropriate for other forms of non-Hodgkin lymphoma should be carried out including bone marrow biopsy and CT of thorax and abdomen. An adequate biopsy is essential for diagnosis and since this is usually performed at laparotomy the opportunity should be taken to assess adjacent organs,lymph nodes and liver, providing this can be done safely. In the case of intestinal involvement skin lesions may occur and their detection is important for future management.

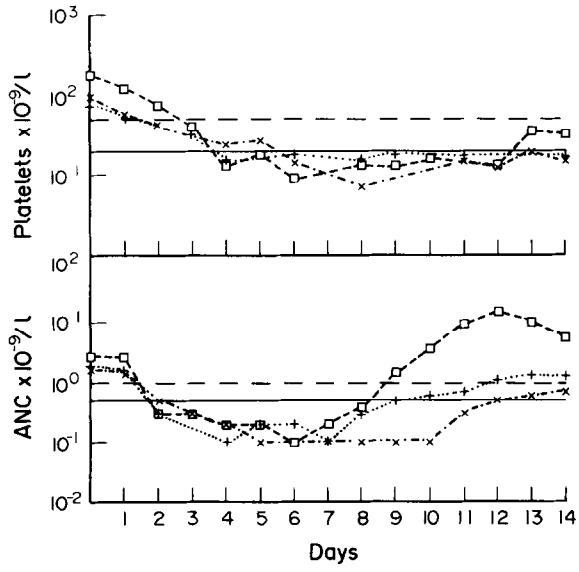

Fig. 4. Engraftment profile of granulocyte and platelet recovery following ablative therapy in 3 patients following autologous bone marrow alone, (+–+) autologous bone marrow transplant and G-CSF (x–x) and this patient following peripheral blood progenitor cells + G-CSF (□–□). Bone marrow or peripheral blood progenitor cells were infused at day 0. G-CSF was given from day 1 to day 11 following reinfusion of the peripheral blood stem cells.

Table 1. Adverse prognostic factors for survival in high-grade non-Hodgkin lymphoma

Stage III and IV disease
Age > 60
B symptoms
Poor performance status
Tumour masses > 10 cm (especially involving gastrointestinal tract)
Multiple extranodal sites
Raised serum lactic dehydrogenase

The gastrointestinal tract is the most common site of extranodal involvement in patients with non-Hodgkin lymphoma. In these patients the disease may remain localised to the primary site and adjacent gastric or mesenteric nodes for a considerable period of time. This phenomenon can be explained by an understanding of lymphocyte physiology [1]. Subsets within the T and B lymphocyte populations have different migratory potential [2] and a clear example of this is the subpopulation of lymphocytes with a special predilection for mucosa-associated lymphoid tissue (MALT). Patients with primary lymphoma of the gastrointestinal tract have a characteristic pattern which is different from patients presenting with nodal lymphomas at more peripheral sites. Unlike most forms of nodal lymphoma these lymphomas frequently remain localised to the gut wall and draining lymph nodes [1, 3], allowing a proportion to be cured using surgery alone. In a series from Manchester, 75% of patients with tumour confined to the gastronintestinal tract and nearly 60% of those with local nodal involvement were cured with local therapy [4]. Of 104 patients in this series only 5% had palpable peripheral adenopathy and in these patients, as in the present patient, the gastrointestinal tract may have been involved as a secondary event. In this patient's case it is unknown whether the disease within the colon was a primary or secondary site of involvement since intestinal involvement may be detected in up to 30% of lymphoma patients at autopsy [5].

Pathology

The strictness of the definition of primary gastrointestinal lymphoma varies between authors [6]. The use of strict criteria in published series is to be recommended in order to avoid the confounding effect of cases with secondary involvement, although this will lead to the exclusion of some primary gut lymphomas.

The gastrointestinal tract is populated by a distinct pool of lymphocytes which shows the ability to recirculate to specific sites within the gut [7]. It is this homing ability which offers an

Table 2. Classification of gastrointestinal lymphomas (synonyms are shown in brackets)

	B cell	T cell
Low grade	Polymorphic B cell, low grade (MALToma, low grade)	Small cell pleomorphic ± enteropathy
	Mediterranean lymphoma (IPSID) Centrocytic lymphoma (malignant lymphomatous polyposis) Others	Others
High grade	Polymorphic B cell, high grade (MALToma, high grade) Burkitt-type lymphoma	Medium/large cell pleomorphic ± enteropathy ± eosinophilia Large cell anaplastic
	Others	Others
	Unclassified	Unclassified

explanation for the propensity of gastrointestinal lymphomas to remain anatomically localised. When dissemination does eventually occur, it may be to peripheral lymphoid tissue or to other mucosal sites [7]. Given the existence of a specific mucosa-associated population of lymphoid cells, it is not surprising that the gastrointestinal tract should give rise to morphologically and immunophenotypically distinct types of lymphoma. Many of these lymphomas are difficult to classify within the classifications, including Kiel, which have been developed for nodal lymphomas. There is increasing agreement that a separate classification is required which reflects the spectrum of lymphoma types commonly found in the gut. A dissenting voice is that of van Krieken [8], who considers that gut lymphomas can be adequately accommodated within the conventional Kiel classification. Among those who agree that a site-specific gastrointestinal classification is needed, disagreement remains as to the best terminology. The most recent version of the classification of Hall and Levison [1] is shown in Table 2.

Isaacson and Wright have proposed the term 'MALToma' for the most common type of lymphoma arising from mucosa associated lymphoid tissue (MALT). This subtype manifests its close interaction with the mucosal epithelium by forming 'lymphoepithelial lesions', a feature which forms one of the cardinal diagostic criteria [7]. Hall *et al.* [9] initially objected to the term MALToma as implying an unproven biological concept. Since 1988, they have modified their position and consider that there is essential conceptual agreement [1]. Nevertheless, they maintain their preference for the descriptive term 'polymorphic B-cell lymphoma' (PBCL); in their opinion the term MALToma should be applied to all lymphomas derived from MALT and not just one subgroup. Hall *et al.* [9] and Isaacson *et al.* [10] concur that PBCL (MALToma) occurs in both low and high grade forms. Hall offers a quantitative criterion [9]: tumours with more than 20% blasts are to be classified as high grade. With sufficient sampling, some tumours can be shown to be a mix of low- and high-grade components [11]. The demonstration of a low-grade component assists in the differentiation of high-grade MALToma from nodal-type high-grade lymphoma. It also suggests that high-grade MALToma may arise by transformation of low-grade MALToma [11].

IPSID (Mediterranean lymphoma, α-heavy-chain disease) may represent a subtype of PBCL with extreme plasmacytic differentiation [1]. Centrocytic lymphoma (malignant lymphomatous polyposis) shows morphological and immunophenotypic similarities to nodal centrocytic lymphoma [1]. It differs from PBCL in commonly being multifocal and in having a poor prognosis. There remain a minority of B cell primary lymphomas of the gastrointestinal tract which do correspond to categories defined for nodal lymphomas; these include both low and high-grade subtypes.

T cell lymphoma commonly, but not invariably, arises in the context of gluten-sensitive enteropathy. Some classifications [10] of T cell lymphoma give primacy to this aetiological consideration, subdividing them into enteropathy-associated T cell lymphoma (EATCL) and others. Hall's classification is morphological, with additional qualifying statements as to the presence or absence of an underlying enteropathy and of eosinophilia. The condition which was known as malignant histiocytosis of the intestine is now recognised to be a T cell lymphoma [12].

Prognostic factors

An overview analysis of prognostic factors for high-grade lymphoma has recently been carried out [13] (Table 1). This study included 1872 patients from 16 cooperative groups or single institutions in Europe and Northern America. These patients with stage I–IV diffuse mixed, diffuse large cell or immunoblastic large cell lymphoma were treated with aggressive combination chemotherapy between 1982 and 1987. For patients less than 60 years of age, three unfavourable features were identified using multivariate analysis (stage III/IV, raised serum lactate dehydrogenase and Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2) which were negatively predictive for complete response, relapse from complete response and survival. The patient described in this paper had all these adverse features.

Patients presenting with symptoms relating to lymphoma involving the gastrointestinal tract have some additional features affecting prognosis. These include bowel perforation, older age, large tumours and involvement of the small or large intestine rather than the stomach [14–16]. The patient described here presented with several of these adverse features. Remission status following chemotherapy induction is a further important variable [17]. In the series treated with chemotherapy in Manchester, the 5-year freedom from progression for the 20 patients achieving complete response (CR) was 79%, whereas only 20% of those with partial remission following initial chemotherapy survived 3 years [14].

Surgery

Deaths occuring in patients with gastrointestinal lymphoma often occur early during chemotherapy and many are related to complications arising from the gastrointestinal tract (haemorrhage, perforation or obstruction) (e.g. [18, 19]). In the Manchester series 21 of 36 patients with gastrointestinal lymphoma died (67% within 6 months of commencing treatment) and 19 of these were from complications arising in the gastrointestinal tract. Where possible removal of the affected segment of the bowel is advised before chemotherapy is given. Surgical resection was not possible in this patient and this has also been identified as an adverse prognostic feature [4, 14, 20, 21].

Chemotherapy

Chemotherapy is indicated for the treatment of intestinal lymphoma in patients unable to undergo complete resection, and can be curative. In order to increase the complete remission and cure rates, there has been an increasing effort to determine the most effective combination and dosage of cytotoxic drugs. Modern regimens comprising alternating non-cross-resistant drugs, some involving weekly chemotherapy, have been reported to be associated with an earlier, higher complete response rate and an improved progression-free survival compared with the earlier CHOP-based (cyclophosphamide, doxorubicin, vincristine, prednisone) regimens. However, randomised trials have yet to show a benefit in terms of overall survival for the newer regimens. These regimens are most appropriate in patients under 60 years with adequate renal, hepatic, pulmonary, endocrine and cardiac function.

Ablative therapy

Attainment of CR is the single most important indicator of prognosis [17, 22–24]. In addition, patients who rapidly achieve CR have a significantly better outlook than those who require prolonged therapy to achieve remission [25]. The use of bone marrow transplantation is intended to circumvent cytotoxic drug resistance by increasing the doses of available cytotoxic agents whilst ameliorating myelotoxicity by infusion of haemopoietic stem cells.

Clearly this patient had chemoresponsive disease, but in view of his poor prognostic factors and the partial response achieved, further therapy was required after induction. The use of autologous bone marrow transplantation for high-grade non-Hodgkin lymphoma in patients with poor prognostic factors has been reported [26, 27]) but no prospective trial comparing autologous bone marrow transplantation with conventional chemotherapy has been completed. Philip *et al.* [28] have reported promising results with a 75% 2-year disease-free survival when high-dose therapy and autologous bone marrow transplanation is performed after obtaining the maximum response to first-line therapy. This suggests that high-dose therapy given while the patient is in remission or has responsive disease (before the development of chemotherapy resistance) results in a significantly better outcome than when given during relapse or after chemotherapy failure in these patients. In a recent review more than half of the patients who underwent transplantation when they had minimal residual disease and who were early in the course of their illness are reported to be alive and well [22, 27].

Ablative therapy with haematologic rescue appears to have a role for selected high-risk groups such as patients with only a partial response (PR) or previous adverse features, although randomised trials are required to confirm this.

Peripheral blood progenitor cell transplantation

Prolonged myelosuppression is a major cause of morbidity and mortality after myeloablative chemotherapy despite autologous bone marrow transplantation, and the cost of supportive measures is high. The use of haemopoietic growth factors can shorten the period of neutropenia [29], reducing the use of antibiotics and duration of hospitalisation, but severe neutropenia and prolonged thrombocytopenia remain. An alternative source of haemopoietic stem cells can be found in the peripheral blood. Autologous transplantation using peripheral blood progenitor cells offers certain advantages including collection of the cells in an outpatient setting, avoidance of general anaesthesia, and feasibility in patients with hypoplastic or malignant infiltration of the marrow who were previously excluded from receiving ablative chemotherapy [30]. The risk of tumour contamination in the cell population used for haemopoietic reconstitution may also be reduced [31–33]. A reduction in early neutropenia and thrombocytopenia postablation has been observed following haematologic rescue with peripheral blood progenitor cells [31, 32, 34, 35]. This is probably a reflection of the large numbers of more committed progenitor cells in the peripheral blood than in the bone marrow, which are capable of producing effective mature cells at an earlier time.

The quantitative problem of low progenitor cell concentration in peripheral blood is overcome by performing leukapheresis during recovery from cytotoxic-induced bone marrow aplasia with or without support by haemopoietic growth factors. Both these treatments increase markedly the number of haemopoietic progenitors in the blood reducing the number of leukaphereses required [34–36]. The ideal release stimulus, optimal collection schedule and threshold dose of peripheral blood progenitor cells required for accelerated recovery and long-term haematopoiesis are not yet defined. For sustained engraftment haemopoietic stem cells must be present and transfused in the harvest. In man, as no unique marker of transplanted cells exist, it is still unclear whether long-term engraftment is of graft origin or from surviving host cells. There are, however, many well-documented cases of long-term recovery postperipheral blood progenitor cell transplant with follow-up to 15 years [30].

Immune recovery as measured by lymphocyte subsets is more rapid following reconstitution using peripheral blood progenitor cells [32]. Some studies indicate more rapid recovery of T cells, natural killer cells and helper/suppressor T cell ratios after blood-cell-derived transplants. In theory, this should reduce the risk of opportunistic infection. Whether or not this can contribute to the antitumour effects (seen with allogeneic bone marrow transplantation) is unclear.

There has been widely expressed concern that neoplastic cells might be mobilised from the marrow into the blood along with haemopoietic stem cells. To reduce this risk, we collected peripheral blood progenitor cells after chemotherapy. In acute leukaemias and high-grade non-Hodgkin lymphoma several different techniques, including cytogenetics and DNA probes, have been unable to detect malignant cells in the apheresis product [31, 32, 37]. Sharp *et al.* [37], using culture techniques to compare directly the frequency of tumour cells in bone marrow and apheresis products, showed a reduced risk of malignant contamination in blood-derived cells in non-Hodgkins' lymphoma patients. Taken together therefore, the data indicate that although there is a risk of tumour cells contaminating PBPC, the likelihood is rather less than that seen with conventional bone marrow autografts.

Peripheral blood progenitor cell autotransplantation appears

to have cost advantage over conventional autologous bone marrow transplantation. The French collaborative group [38] showed a 50% cost saving including all parameters such as harvesting, cryopreservation, chemotoxic agents, antibiotics, transfusions and professional (medical and nursing time). Patients and hospitals will seek to benefit from the reduced hospital stay required for this novel approach to intensive treatment. Nevertheless, the value of intensified treatment strategies requires full evaluation in controlled studies.

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