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Letters to the editor

Hepatocellular carcinoma in a patient with Gaucher disease on enzyme supplementation therapy

Gaucher disease is an autosomal recessive disorder characterized by the deficiency of the lysosomal enzyme glucocerebrosidase. Accumulation of glucocerebroside occurs in macrophages leading to hepatosplenomegaly and bone marrow infiltration with consequently cytopenia and bone disease (type I Gaucher). Neurological disturbances are rare and have a rapidly fatal (infantile, type II) or chronic progressive (juvenile, type III) course [1]. In 1991 the first series appeared about enzyme supplementation therapy [2], followed by the experience from other centers [3]. Over the last years more than 1500 patients received or are receiving enzyme replacement therapy. This therapy consists of alglucerase or imiglucerase injections. Alglucerase is purified from a pool of placental tissue collected from several donors and therefore human chorionic gonadotrophin (hCG) is present in this product. The recently developed imiglucerase is produced using recombinant DNA technology.

Increased risk of malignancy in patients with Gaucher disease has been observed [4]. It has been hypothesized that this might be due to a defective immune surveillance due to chronic stimulation as consequence of accumulation of glucocerebroside in macrophages, T-cell dysfunction resulting from high levels of ferritin or from a factor released from monocytes. Hematological malignancies are predominant (myeloma, lymphatic leukemia, lymphoma), solid tumors are rare. Hepatocellular carcinoma (HCC) was reported once in a type I Gaucher disease patient with cirrhosis and hepatitis B, in which both diseases were suggested as possible causative factors for the malignancy [5]. We report a case of HCC in a 62-year-old Caucasian male, known with Gaucher disease type I. His disease was characterized by hepatosplenomegaly and bone and joint.destructions. In 1988 severe leuco- and thrombopenia developed due to hypersplenism which resolved after splenectomy. Because of progressive bone destruction resulting in a serious mobility impairment, he was offered therapy with alglucerase. He has received weekly 15 U/kg from April 1995 till November 1996. No side-effects occurred and he responded well, as judged by a decrease in liver volume. In December 1996, ultrasound and computed tomography of upper abdomen, performed because of persistent pain in the right upper abdomen, revealed an echodense lesion in the left liver lobe. Diagnostic laparotomy revealed metastatic lesions in peritoneum, omentum and tumor in the left liver lobe. Histological examination showed HCC cells in all specimens. At the moment of HCC diagnosis, laboratory test showed normal liver synthesis (ATIII 92%, cholinesterase 2100 IU, albumin 41 g/l), negative hepatitis B serology, normal immunoglobulin electrophoresis and elevated α-foetoprotein (AFP) of 89.000 μg/l.

There were no known predisposing factors for HCC. Retrospective analysis of blood samples, taken every six months, revealed that the AFP level prior to the start of alglucerase therapy was normal (3 μg/l). Six months later it was slightly elevated (11 μg/l) and showed further rise (101, 36500, 83628 μg/l) in following samples. The increase in AFP during the supplementation therapy suggests a possible relation with the alglucerase treatment and thus simultaneous long-term exposure to hCG. In alglucerase, hCG is partially deglycosylated during the production process and cleared at a higher rate than native hCG. However, its *in vivo* biological activity is yet unclear. HCC's often express hCG. Occurrence of HCC during pregnancy has been reported and oral contraceptives are a risk factor for its development. It could be speculated that exogenous administered hCG might serve directly as growth factor in inducing HCC or play an indirect role by modification of other hormones. Imiglucerase as a recombinant DNA product does not contain hCG. Another option is that occurrence of HCC in this patient is merely due to prolonged compromized immune surveillance secondary to macrophage dysfunction. The fact that HCC has never been reported in Gaucher disease patients without risk factors and that enzyme supplementation therapy is new, justifies attention for the potential carcinogenic effect of hCG alglucerase therapy. It might be relevant to check AFP levels during this therapy in order to evaluate whether other patients also develop a HCC and, if so, to reveal this at an early stage.

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Cost comparison between PAV and ICE treatment with peripheral blood progenitor cells (PBPC) reinfusion in small-cell lung cancer (SCLC)

High-dose chemotherapy with reinfusion of autologous hematopoietic progenitors has improved the prognosis of patients with lymphomas [1]. For patients with small cell lung cancer (SCLC), early intensification with ICE (ifosfamide, carboplatinum, etoposide) resulted in a median survival of 19 months for patients with limited disease (LD) and 10 months for patients with extensive disease (ED) [2]. The standard PAV regimen (cispla-

tinum, adriamycine and etoposide = VP16) results in a median survival of 12 months (15 for LD and 10 for ED patients) [3].

The costs of the two regimens were compared in four patients treated with PAV (two men and two women, one LD and three ED, median age: 60 years, range 48–70) and four patients treated with ICE and PBPC reinfusion (three men and one woman, two LD and two ED, median age: 61 years, range 41–63).

The chemotherapy regimens were as follows: PAV (platinum: 30 mg/m^2, days 1–3; adriamycin: 40 mg/m^2, day 1 and VP16: 100 mg/m^2, days 1–3) was administered every 28 days for six cycles. The ICE regimen included two phases: PBPC mobilization with epirubicine (150 mg/m^2 over two days) followed by filgrastim (5 μg/kg/day) until leucaphereses completion. ICE consisted in ifosphamide (2.5 g/m^2/day, continuous infusion for four days), carboplatin (300 mg/m^2/day) and etoposide (300 mg/m^2/day) days 1–4, followed by reinfusion of PBPC and filgrastim (5 μg/kg/day) until leucocyte recovery. Three cycles were administered at monthly intervals.

Cost identification was carried out as follows: physician, nurse, secretarial and administrative times were estimated for each patient specifically according to the data provided by multiple sources. Blood, platelets transfusions and drugs were valued at cost price; laboratory tests, paramedical services and external consultations at price charged. Overhead was extracted from the cost accounting system.

The hospital stay was 36 ± 5 days in the PAV group and 59 ± 2 days in the ICE group. The break down of costs per treatment phase, per nature of expenses and the comparison between treatments is shown in Table 1. Intensification chemotherapy with PBPC reinfusion for treatment of SCLC was 2.4 times more expensive than traditional PAV treatment, due to longer hospital stay, more febrile neutropenia, higher drug acquisition costs, and greater platelets and red cells transfusion needs.

This cost comparison study was based on too few patients to analyze their survival. The recent multicentric phase II trial with sequential ICE and other recently published results using growth factors [4] suggest that intensifying chemotherapy in SCLC patients may increase the number of long survivors. However, in order to remain within the cost-benefit ratio usually accepted for medical interventions, the difference in cost between the two treatments should not exceed $50,000/life-year saved or quality-adjusted life-year saved (QALY) [5]. In our setting, this implies that survival would have to increase by a full year.

High-dose chemotherapy followed by PBPC in SCLC patients is presently evaluated in a randomized phase III study supported by the EBMT. Cost analysis and cost/benefit ratios will undoubtly help delineating the clinical role of this approach.

Table 1. Break down of costs by treatment phase and type of resources.

	PAV group (n = 4)	ICE group (n = 4)	ICE/PAV ratio
Cost per phase (mean ± SEM)			
Pre-treatment	0	641 ± 0	–
Chemotherapy	34,883 ± 5,601	85,138 ± 3,438	2.4
Febrile neutropenia	9,341 ± 7,645	31,667 ± 4,136	3.4
Outpatient visits (one month)	5,498 ± 748	3,353 ± 752	0.6
Cost per type of resources (mean ± SEM)			
Physician time	4,478 ± 389	5,978 ± 55	1.3
Nursing time	14,779 ± 1,718	34,986 ± 505	2.4
Administrative time	1,076 ± 99	1,124 ± 50	1.0
Laboratory tests	4,801 ± 818	17,490 ± 1,607	3.6
Other paraclinic tests	5,880 ± 1,163	7,844 ± 426	1.3
Drugs	7,496 ± 373	26,150 ± 3,438	3.5
Blood products	330 ± 270	9,358 ± 687	28.4
Other direct charges	2,018 ± 237	3,654 ± 119	1.8
Indirect charges	8,865 ± 1,319	14,216 ± 437	1.6
Total cost (CHF)	49,721 ± 4,617	120,798 ± 4,401	2.4

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A specific approval procedure for prescribing albumin: Impact on consumption in a cancer treatment institution

Albumin solution is a natural colloid solution which is mainly indicated for hypovolemia and osmotic pressure disorders. Alternative, equally effective treatments, such as crystalloid or synthetic colloid solutions are available at a lower cost [1].

Until 1994, our 500-bed cancer treatment institution was devoid of a system for channeling albumin consumption. In January 1995, the hospital's executive committee entrusted the Transfusion and Hemosurveillance Safety Committee (THSC) with the responsibility of rationalizing albumin consumption. The hospital hemobiologist, a THSC member in charge of transfusion, proposed institute-specific guidelines defining very limited indications for albumin based on current knowledge [2, 3]. These guidelines were validated by three other physicians in the institute and by an outside expert and were then approved by all THSC members and the institute Medical Affairs Manager. A letter was sent to all physicians informing them of these recommendations in March 1995. Subsequently, albumin prescriptions were systematically vetted, according to these recommendations, by the hemobiologist who then contacted the prescriber to check and validate each prescription before delivery of albumin.

Results of the rationalization procedure are presented in Table 1. Between 1994, the baseline year before implementation