Letters to the editor

Costs of autologous stem-cell transplantation in solid tumours

In the May issue of Annals of Oncology (2000, 11 603-6) Dr Astier and co-workers report on the costs of high-dose chemotherapy (HDC) and autologous peripheral blood stem-cell transplantation (APBSCT) in patients with solid tumours. The authors analyse in great detail the direct and indirect costs of the procedure in 27 consecutive patients treated in a single institution and conclude that the mean overall cost is 21,445 US dollars. The results obtained by the Spanish study are in accordance with previous reports and our own experience (see below).

All the cost-analyses regarding APBSCT have so far considered stem cell support following high-dose, myeloablative chemotherapy. However, in recent years this approach has been increasingly used with less intensive chemotherapy regimens. In particular, critical economic issues are raised when PBSC reinfusion is used solely as a supportive (sometimes cosmetic) measure following non-myeloablative courses of chemotherapy [1, 2]. In those cases the procedure, often within multiple transplant programs, is also feasible and safe in the outpatient setting. In contrast, myeloablative chemotherapy usually requires extended hospitalisation, intensive nursing care and expensive supportive measures.

We evaluated the overall costs of four different approaches of autologous transplantation, two including a myeloablative regimen [3, 4] and two following 'intermediate-dose' treatments [1, 2]. As expected our data show a wide range of resource utilisation among different approaches of APBSCT (Table 1) which relate to the intensity of the chemotherapy regimen delivered. From the economic point of view it would be interesting to know how these procedures are reimbursed throughout Europe.

In fact, the ICD9-CM classification system, which is utilised in most European countries, considers one possible procedure (autologous hematopoetic stem-cell transplantation 41.04, DRG 481) which can be used in this clinical setting. Reimbursement by the National Health Service, at least in Italy, for DRG 481 is adequate to cover the costs of myeloablative with APBSCT. However, the use of code 41.04 for such less expensive, non-myeloablative, chemotherapy regimens (often multiple) may represent an easy way to balance hospital budgets and cause additional costs for National Health Services in most European countries, considers one possible procedure (autologous hematopoetic stem-cell transplantation 41.04, DRG 481) which can be used in this clinical setting. Reimbursement by the National Health Service, at least in Italy, for DRG 481 is adequate to cover the costs of myeloablative with APBSCT. However, the use of code 41.04 for much less expensive, non-myeloablative, chemotherapy regimens (often multiple) may represent an easy way to balance hospital budgets and cause additional costs for National Health Services.
Idiosyncratic reaction after oxaliplatin infusion

Oxaliplatin (L-OHP) is a new alkylating platinum compound with proven cytotoxic activity; it is used as a single agent in different types of cancer and in combination with 5-fluorouracil (5-FU) and folinic acid (FA) in colorectal carcinoma. The overall incidence of grade 3–4 (NCI-CTC) haematological toxicity is 11%, gastrointestinal toxicity 20%, neurotoxicity (all grade 3) 2%–3% and death from treatment-related toxicity about 1%–2% [1].

For the first time we describe a case of a 52-year-old man who twice developed an idiosyncratic reaction after L-OHP administration. In January 1998 the patient underwent resection of a rectal cancer and wedge-resection of a synchronous liver metastasis; after surgery he received six cycles of chemotherapy with 5-FU and FA. In October 1999 multiple bilateral pulmonary recurrences were found by CT-scan and therefore a chemotherapy with weekly (w) L-OHP–5-FU–FA infusions was started with the following doses L-OHP 60 mg/m²/w; FA 20 mg/m²/w and 5-FU 600 mg/m²/w; all drugs were administered for 3 consecutive weeks every 28 days. In the clinical history there was no evidence of allergy to drugs or atopic diseases and the patient did not present any relevant co-morbidity, in January 2000 he developed a drug-induced diabetes related to prophylaxis with steroids.

Fifteen to twenty minutes after the end of L-OHP infusion, during the third and sixth cycle of treatment, the patient had an unusual idiosyncratic reaction to chemotherapy, in both cases the patient did not receive pre-treatment with dexamethasone because of diabetes the first time and due to a misunderstanding the second time. Symptoms that occurred were chills, fever (39.3 °C), nausea, vomiting, crampy abdominal pain, diarrhoea and hypotension (90/60 mmHg).

The first time reaction resolved after one hour, except body temperature which decreased to within normal range after five hours. The second time, 10 minutes after the beginning of the reaction, dexamethasone (8 mg i.v) was administered with prompt regression of reaction, only fever persisted for about 4 hours. In both cases laboratory tests were performed and did not show significant alterations, in particular, total bilirubin (0.8 mg/dl) and reticulocytes count (2.5%) were within normal range and a haemolytic reaction was excluded [2]. In the last episode serum levels of Interleukin-6 (IL-6) and Tumor necrosis factor-alpha (TNF-α) were elevated (IL-6 220 pg/ml; TNF-α 352 pg/ml) during clinical manifestations, while such cytokine levels significantly decreased when the symptoms disappeared (IL-6 32 pg/ml, TNF-α 28 pg/ml).

To our knowledge this is the first report in literature of a L-OHP-induced idiosyncratic reaction. The absence of laryngospasm, pruritus, and severe hypotension lead us to exclude an anaphylactic reaction to this drug [3]. Moreover, since the occurrence of chills, fever, diarrhoea, crampy abdominal pain, nausea, vomiting and mild hypotension was associated with high levels of cytokines and a complete regression of reaction after administration of steroids, a cytokine-release syndrome [4] induced by L-OHP infusion may be supposed in our patient. We can speculate that L-OHP acted as a superantigen, causing lymphocyte over-activation and massive cytokine release; superantigens stimulate T-cell proliferation and cytokine production by direct binding to major histocompatibility complex (MHC) class II molecules on antigen-presenting cells with subsequent stimulation of T cells. In vivo and in vitro studies demonstrated that superantigens induce release of pro-inflammatory mediators, including TNF-α, γ-interferon, IL-1 and IL-6, so causing chills, fever, abdominal pain, diarrhoea and vomiting as occurred in our patient [5-7]. According to our hypothesis, an idiosyncratic reaction occurred only when prophylaxis with steroids was not performed. In our opinion this knowledge may be helpful in clinical care and a pre-medication with steroids may be recommended before administration of L-OHP if a similar reaction has occurred in a previous cycle.