A new approach to safeguard high standards and cost containment of stem cell transplantation in Germany

Due to the tight budgets of the German public health insurances (PHI), new and expensive medical services have come under increased scrutiny since the mid-90s. Not surprisingly, this also applies to stem cell transplantation (SCT). In 1996, more than 250 hospitals applied for licence to perform SCT in Germany, raising fears of deteriorating standards and a cost explosion, especially as new indications such as breast cancer emerged.

To solve this problem the Concerted Action Stem Cell Transplantation (CASCT) was created. It comprises several scientific societies (German Society of Hematology and Oncology, Association of Internal Oncology, German Working Group for Bone Marrow and Stem Cell Transplantation, German Societies of Pediatric Oncology and Hematology, Radiological Oncology, Transfusion Medicine, Gynaecology and Urology) and the PHI. The following steps have been taken by CASCT:

1) Official and binding standards and guidelines for SCT were laid down and published in cooperation with the German Chamber of Physicians. 2) Expert assessments are carried out at institutions wishing to provide SCT. The costs of the site visits (approx. $6,000 per assessment) are borne by the applying institutions. So far, 45 centers have applied and 19 have been examined. Of these, only five were awarded the certificate which is a prerequisite for reimbursement of SCT by the PHI.

3) Indications for auto SCT have been agreed with the PHI. They include, apart from leukemias and lymphomas, breast and ovarian cancer, small cell lung cancer (limited disease) and germ cell tumours. 4) A national registry for SCT has been created and currently collects data following EBM/ Med A standards of all SCT in Germany. 5) Data from the registry will be published yearly. 6) Cost–benefit-analyses relating to SCT will be carried out, taking into account both clinical effectiveness and cost data.

In our view CASCT is an innovative attempt to reconcile expensive advances in oncology with quality assurance and cost-control. However, the steps agreed grant substantial power to the PHI, including involvement in the choice of providers of SCT and in establishing indications. At this stage, the long term consequences of this are unclear and will require further investigation.

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Gemcitabine: A real major advance?

We read with interest the editorial comment on gemcitabine by Thomas and Stewart [1] and we appreciate their prudent conclusion that gemcitabine is an 'important' new agent (implicitly not a 'major advance'). The editorial stimulates us once again to express our philosophy on the correct way to evaluate a new antineoplastic agent [2]. In fact, to evaluate a new drug we should distinguish between the cancer outcomes – complete and partial response, response duration, time to disease progression – which can be regarded as activity indexes, and the patients' outcomes – survival and quality of life – which can be considered as indexes of effectiveness [3]. Patient outcomes must be considered the main endpoints of every phase III clinical trial and the only parameters by which to identify the best antineoplastic treatment and the advances achieved by the new treatment.

With respect to survival, only one comparative study versus fluorouracil showed a statistically significant improvement with gemcitabine [4], but the increase in median survival was only five weeks; this difference might be attributable at least in part to the greater (although not significant) prevalence of stage II pancreatic cancer in gemcitabine-treated patients than in those who received fluorouracil [2].

With respect to quality of life, no comparative studies on gemcitabine, using formal and validated questionnaires, have yet been published. Due to the difficulty in assessing and interpreting quality of life results, the concept of 'clinical benefit' as a new patient's outcome has been developed. Clinical benefit addresses the beneficial effects of a treatment in improving disease-related symptoms and signs (pain, performance status, weight).

Thomas and Stewart acritically stated that "the novel endpoint of clinical benefit response has been a welcome development to a more clinically relevant outcome measure". Unfortunately, there are important shortcomings in using clinical benefit as an outcome [2]: 1) Any clinical benefit always must be weighted against the treatment's toxicity. Chemotherapy induces adverse events that even when mild can have a negative impact on a patient's quality of life. In the study evaluating clinical benefit response, patients who received gemcitabine had more grades 3 and 4 neutropenia and fever than patients who received fluorouracil. Therefore, to correctly evaluate the chemotherapy impact, it would be important to adjust clinical benefit to the adverse events, but this has not been done [3]. 2) Due to the subjectivity in evaluating the responses, a double-blind trial should be carried out, but this is impossible when chemotherapy is one of the arms of the study, and 3) The clinical relevance of clinical benefit should be interpreted with caution. In fact, clinical benefit has not been validated, nor is a comparison available with validated instruments by which to measure the quality of life [4]. Thus, there is serious doubt as to its scientific and clinical value as a patient-outcome parameter. Considering all these factors, and taking into account the cost, we conclude that gemcitabine should be used sparingly until new data based on harder evidence (survival and quality of life) are provided by ongoing clinical trials. These conclusions are probably valid not only for gemcitabine but also for most of the new antineoplastic agents recently made available.

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A 63-year-old man presented with a stage D Dukes colon adenocarcinoma with liver metastases. He underwent palliative hemicolectomy and then received a chemotherapy regimen of 5-fluorouracil (5-FU) and folinic acid (FA). Six treatment cycles were administered with satisfactory tolerance but progression of the disease led to the addition of oxaliplatin (100 mg/m²/cycle) to the above described regimen. Grade I paresthesia was noted during the second cycle and a brief episode of laryngospasm during the third cycle which, however, resolved spontaneously. During the sixth oxaliplatin infusion, before the 5-FU and FA administrations, the patient complained of a painful and widespread feeling of burning and diffuse pruritus, visual disturbances, facial and lingual edema, tachycardia and severe hypotension. Anaphylactic shock was diagnosed. The patient received injections of methylprednisolone and adrenaline to which he completely responded within a few minutes. His blood count revealed 4100 white blood cells of which 3.4% were mastocytes.

There are few published reports of allergic reactions after oxaliplatin use. De Gramont et al. noted hypersensitivity similar to anaphylaxis in 1 of 46 patients during the sixth treatment cycle [3], Machover et al. encountered one case of dyspnea of undefined origin in two phase II studies in 109 patients [4], and Weiss and Christian have described the possibility of treatment-related pharyngospasm [5].

Although oxaliplatin is a well-tolerated cytotoxic agent, we recommend that it be administered in an appropriate environment under strict medical surveillance. The drug should not be re-introduced even when the allergic manifestations observed were weak.

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References


Anaphylaxis after oxaliplatin

Oxaliplatin (L-OHP) trans-1-diaminocyclohexane-oxaloplatinum) is a platinum complex with proven cytotoxic activity [1, 2]. It has become a standard drug in France for the treatment of colorectal cancers. A few allergic reactions have been described but they have not been severe [3-5].

We report a case of anaphylactic shock secondary to treatment with oxaliplatin.

A 63-year-old man presented with a stage D Dukes colon adenocarcinoma with liver metastases. He underwent palliative hemicolectomy and then received a chemotherapy regimen of 5-fluorouracil (5-FU) and folinic acid (FA). Six treatment cycles were administered with satisfactory tolerance but progression of the disease led to the addition of oxaliplatin (100 mg/m²/cycle) to the above described regimen. Grade I paresthesia was noted during the second cycle and a brief episode of laryngospasm during the third cycle which, however, resolved spontaneously. During the sixth oxaliplatin infusion, before the 5-FU and FA administrations, the patient complained of a painful and widespread feeling of burning and diffuse pruritus, visual disturbances, facial and lingual edema, tachycardia and severe hypotension. Anaphylactic shock was diagnosed. The patient received injections of methylprednisolone and adrenaline to which he completely responded within a few minutes. His blood count revealed 4100 white blood cells of which 3.4% were mastocytes.

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