bone marrow transplants, to minimally processed cell gafts, to manipulated cell transplants.

The EBMT has elaborated Standards for specialist units undertaking blood and marrow stem cell transplants (Bone Marrow Transplantation 16: 733–736, 1995), Standards for Blood and Marrow Progenitor Cell Processing, Collection and Transplantation (EBMT Operational Manual 1998), in collaboration with ISHAGE and Standard Indications in 1998 (Allogeneic and autologous transplantation for haematological disease, solid tumours and immune disorders: current practice in Europe 1998 (Bone Marrow Transplantation, 21: 1–7, 1998).

1223

Hematopoietic stem cell transplants (HSCT) in leukemia in Europe

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Hemopoietic stem cell transplantation is increasingly utilized for the treatment of leukemia. In the EBMT file there are registered 22,000 transplants for acute leukemias (AL), 9500 for chronic myeloid leukemia (CML), 2600 for myelodisplasia (MDS) and 450 for chronic lymphocytic leukemia (CLL). The results have improved considerably over time. Allogeneic (A-HSCT) between HLA compatible sibling for AL has reduced the transplant related mortality (TRM) from 40% to 20% if performed in 1CR; the leukemia free survival (LFS) after 1990 for acute myeloid leukemia (AML) exceeds 60% at 5 years. In most studies A-HSCT has shown to be never inferior to other therapeutic options. Current results of Autologous (AU-HSCT) for AML indicate approximately 45–50% LFS. AU-HSCT has been demonstrated superior to chemotherapy in the majority of randomized studies conducted on intent-to-treat basis. For acute lymphoblastic leukemia (ALL) the LFS after A-HSCT is 55% at 5 years. The role of autograft in ALL is unclear. Matched Unrelated donor (MUD) transplant results are improving; for AL patients beyond second remission, A-HSCT or MUD transplant represents, in adults, the only chance of cure. For CML patients, A-HSCT remains the only proven curative approach. A-HSCT from an HLA compatible sibling is able to produce 50–65% LFS. The trend in CML is to reduce the toxicity of the conditioning regimen in view of the efficacy of donor lymphocyte infusion (DLI), capable of rescuing 70% of relapsed patients. Matched unrelated donor (MUD) transplant are expanding and the results are rapidly improving; however, in view of the results with IFN treatment, the therapeutic choice for low Sokal risk patients remains difficult. For MDS HSCT can provide a possibility of cure although these patients are very fragile and adjustments in the conditioning regimen are needed. In the next years we shall know the role of HSCT in CLL.

1224

Bone marrow transplantation for multiple myeloma

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The place of stem cell transplantation in the management of myeloma remains controversial. The largest body of data relating to allogeneic transplantation has been collected by the EBMT registry and totals over 400 patients transplanted at various stages of the disease. Overall there is a high transplant related mortality of 30–40% and relapse incidencer of over 50%. However the survival curve beyond 5 years approaches a plateau, with a projected long-term survival for all patients of around 35%. In a multivariate analysis of pre-transplant features, two were identified as found to be poor prognostic factors i.e. transplant after more than one line of therapy and male gender. More recent results from the registry show that overall survival has improved over the last 5 years. Autologous transplant is now an extremely safe procedure for patients under the age of 65 years. However autografting is not curative with a median event free survival of about 2 years. A number of randomised studies have been designed to address the potential benefit of autografting over conventional therapy. The results of one such study, by the French IFM group have shown a survival benefit with the 5 year overall survival and EFS of autograft recipients being 52% and 28% compared to 12% and 10% in patients treated conventionally. A subsequent study from this group compared a single transplant with a double procedure. At this time there is trend in favour of two procedures for patients with normal β_2M levels at diagnosis. Patients with high β_2M concentrations tend to do poorly with all current forms of therapy and more innovative approaches are required for this group of patients.

1225

High-dose chemotherapy in lymphoma

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Lymphoma is the most frequent disease of patients undergoing high-dose therapy (HDT) followed by transplantation of hemopoietic stem cells (HSC) in Europe. The Working Party (WP) Lymphoma of the EBMT currently contains information on 20455 patients (pts) transplanted between 1978 and 1999. The diagnoses of these pts were: high-grade NHL (n = 3890, 21.3%), intermediate grade NL (n = 3184, 17.4%), low grade NHL (n = 2404, 13.2%), lymphoblastic lymphoma (n = 1761, 9.7%), Burkitt lymphoma (n = 524, 2.9%), unclassified NHL (n = 1171, 6.4%), or Hodgkin's disease (n = 5314, 29.1%).

The status of the disease at the time of transplantation was: CR1 (n = 3976, 21.3%), CR2 (n = 3235, 17.3%), CR $\geq$ 3 (n = 735, 3.9%), PR (n = 3605, 19.3%), VGPR (n = 1350, 7.2%), untested relapse (n = 748, 4%), sensitive relapse (n = 2595, 13.9%), resistant relapse (n = 1147, 6.1%), primary refractory disease (n = 1248, 6.7%), at diagnosis (n = 19, 1%). 11611 (62.4%) pts received autologous HSC and 328 (20.1%) pts received allogeneic HSCs; a major switch from bone marrow to peripheral blood stem cells as the source of hemopoietic stem cells occurred during the last decade. 1405 (18%) of all autologous grafts were purged by various methods. Overall survival and progression-free survival of pts vary widely with the type of lymphoma and the status of disease at the time of transplantation. Within the major disease categories status of disease was the overriding prognostic factor determining the success of the transplant. As with other diseases there are few prospective randomised trials directly comparing the results of HDT/transplantation with conventional therapy. EBMT together with the German Hodgkin's Lymphoma Study Group has recently analysed such a trial for pts with relapsed Hodgkin's disease; other trials are currently accruing pts.

1226

Lights and shadows in high-dose chemotherapy for solid tumours

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HDC is being offered to an increasing number of patients with solid tumors as in Europe as in North America. In 1997 nearly 2,600 patients with breast cancer received this treatment modality in Europe (60% with high-risk primary disease). In the last decade autologous marrow has nearly universally been replaced by PBPCT (peripheral blood progenitor cells transplantation) and toxic death rate has decreased from 15–18% in the mid and late eighties to the present 1–2%. The reasons might lie in the use of PBPC, hematopoietic growth factors, better knowledge of the procedure, but certainly also to a better patients' selection. In the treatment of high risk breast cancer (>10 positive nodes) several phase II studies have produced 3–5 year disease free-survival in the range of 50–70% which seems to compare favorably with the results achievable with standard anthracycline containing regimen even if conflicting results have been presented at the 1999 ASCO meeting so we still have to wait for more mature follow-up. For metastatic disease, patients intensified in CR1 show 30% DFS at 3 years from registry data. More unclear and non-homogenous results have been produced in ovarian cancer and SCLC, while for germ cell tumors data from the EBMT show a 50% DFS for patients autografted in sensitive relapse. Is more better? The answer is coming out from randomized phase III studies, but the definitive one has not yet be given. Other open questions are: Which drugs? Which regimens? Which strategies?

1227

Bone marrow transplantation in children

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Allogeneic transplantation (BMT) or better hematopoietic stem cell transplantation has been used successfully for the first time in 1968 in children with severe combined immunodeficiency. Since that time, inborn errors of the function of the immune system can be corrected by this procedure. In the meantime it is used also for the correction of inborn defects of the myelopoiesis, erythropoiesis, osteoclasts, osteoblasts, and monocytes, as well as for aplastic anemia. In pediatric ontology the indications for allogeneic BMT are very much dependent on the success rate of conventional

chemotherapy. E. g. 70% of the children with acute lymphoblastic leukemia can be cured by conventional chemotherapy. This is also true, but to a lower degree, for acute myelogenic leukemia. The conventional results of the treatment of M. Hodgkin and NHL are even better than those in ALL. For most solid tumors good results can also be obtained with the combination of surgery, chemotherapy, and radiotherapy. This is why the indication for autologous BMT is limited to metastatic tumors. High-dose chemotherapy (HDC) with stem cell rescue can cure some of the children. In general, one can say that tumors which are not responding to conventional doses of chemotherapy do not benefit of HDC. BMT is an important factor of therapy in pediatric oncology. However, it is needed only in a limited number of children with cancer. Recently the use of parents as haploidentical donors has appeared to be a possibility even for those children who lack an identical sibling or an unrelated matched donor.

1228

The role of prognostic factors in the management of epithelial ovarian carcinoma

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Prognostic factors predict outcome in many ways including survival, response to therapy, etc. Their role is continuously increasing in individualizing treatment, and thereby avoiding under- and over-treatment. Staging is actually the anatomical extension of the tumor and per se is a prognostic factor. The major concerns in the management of epithelial ovarian carcinoma include: 1. the need for adjuvant chemotherapy in early-stage ovarian carcinoma, 2. the place of lymphadenectomy, 3. the role of neoadjuvant chemotherapy in advanced-stage ovarian carcinoma, 4. surgical radicality, 5. selection of drugs, and 6. novel treatment modalities. Using molecular biology techniques in testing the underlying genetic mutations in the tumors of individual patients, i.e. applied genetic testing, we have been able to identify more and more new independent prognostic indicators in terms of outcome, therapeutic effectiveness, etc. In most instances, the role of these novel prognostic factors in the management of epithelial ovarian carcinoma has yet to be determined. Some of them, however, appear to have a place. Their possible therapeutic implications will be discussed.

1229

Surgical dilemma in the management of epithelial ovarian carcinoma

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Surgical dilemmas in the management of epithelial ovarian cancer involve: 1) role of conservative treatment on the uterus and controlateral ovary in young women with very early stages; 2) role of lymphadenectomy as part of complete surgical debulking in advanced stages; 3) role, advantages and limits of primary surgery in grossly bulky late stage III and IV stages; 4) role of surgical reesploration in patients optimally debulked after completion of first line chemotherapy; 5) role of surgery in converting a partial response to chemotherapy in a complete response; 6) role of second surgical effort. Clinical trials are now on-going trying to clearly these problems. Unfortunally surgical clinical trials often soffer of difficulties related to different percentage of patients optimally debulked in any single Institutions, different attitude, towards maximal surgical effort in primary surgery, of the surgeons different opinions concerning second surgery in the general plan of treatment in patients with advanced stages.

1230

The role of neoadjuvant chemotherapy in advanced ovarian carcinoma

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Recently, neoadjuvant chemotherapy (NCT) has been reported in patients with advanced ovarian carcinoma (8 studies; total n = 438). These studies suggest that the same survival with a lower operative morbidity can be obtained with NCT compared with primary debulking surgery (PDS).

In our own study on 338 patients with Stage III or IV ovarian carcinoma the actuarial crude survival was higher in the period in which we administrated NCT in 44% of the patients then in an earlier period in which PDS was performed in all patients (3 year crude survival 37% and 26%, respectively; $p = 0.05$). Selection of NCT or PDS was mainly based on the possibility to debulk the patient primarily to no residual tumor (no residual tumor in 90% of the group with PDS). The EORTC recently started a prospective randomised study in which patients with ovarian cancer Stage IIIc or IV are randomised between PDS followed by 6 courses of platin-taxoid based chemotherapy (Arm A) versus NCT (same as Arm A) with interval debulking surgery (IDS) after 3 courses. The results of this randomised study must be awaited before the role of NCT followed by IDS in advanced ovarian cancer can be established.

1231

Current trends in the management of epithelial ovarian cancer

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The GOG conducted three prospective randomized trials of adjuvant therapy in patients with localized ovarian cancer (OC). In patients with stages Ia and Ib (G1–G2) OC there were no significant diferences between the patients given no CT and those treated with melphalan. In stage I tumors (G3) or stage II treatment with either melphalan or a single intraperitoneal dose of 32P was similar with respect to 5-year disease-free survival and overall survival. In the third trial stage I and II patients received 3 cycles of CP compared with intraperitoneal 32P. The results of this trial will be presented shortly and it seems that CP is more effective than 32P. The EORTC is now closing a randomized trial for stages I and IIa OC patients comparing the adjuvant CT, with a regimen containing cisplatin or carboplatin, versus no adjuvant treatment. In advanced ovarian cancer (ADVOCA) cisplatin-based combination chemotherapy regimens have produced response rates of 60% to 80% and a median overall survival of approximately 20 months. Before taxol was used in the treatment of patients with ADVOCA, cisplatin was considered the best drug. Most prospective studies comparing a "standard" dose of cisplatin "versus" a dose intensification were not able to show any differences concerning survival in favor of cisplatin dose intensification. Clinical comparisions of carboplatin and cisplatin as single agents or in combination have yielded comparable results. The GOG has conducted a randomized clinical trial comparing paclitaxel and cisplatin (TP) with CP in suboptimally debulked stages III and IV patients. There was a statistically significant improvement in the clinical response rate in the TP arm and median survival was also significantly better in the TP arm. A confirmatory trial has been run in Europe and Canada and the data are similar to GOG trial. TP is now considered to be the preferred combination regimen. There is no consensus about the treatment of patients with OC in PCR after second-look surgery. The main options are: wait-and-see; maintenance therapy using three to six more cycles of the same induction CT; whole abdominal radiation therapy; high-dose CT followed by autologous bone marrow transplant; intraperitoneal CT. None of these modalities has proved a clear and definitive advantage in terms of disease free survival or survival.

1232

Abstract not received.

1233

New approaches in the management of ovarian cancer

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Although the tests of treatment with conventional chemotherapy are gradually improving, the majority of women with epithelial ovarian cancer still die of the disease. A range of new approaches to treatment are therefore under active investigation. These are largely based on a rapidly expanding body of information on the molecular and genetic make-up of the ovarian cancer cell itself, its interaction with surrounding stroma, and the basis for resistance to chemotherapy. The approaches thus include:

- agents designed to circumvent drug resistance including novel cytotoxics.
- signal transduction inhibitors, and new forms of hormone therapy
- angiogenesis and matrix metalloproteinase inhibitors
- immunotherapy, immunotoxins and radioconjugates
- new forms of (intraperitoneal) gene therapy.

All of these approaches will need to be used in conjunction with conventional chemotherapy, which itself will be augmented by the addition of newer agents, e.g. topotecan, gemcitabine, preferably in imaginative (sequential) schedules.