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# High-dose Chemotherapy in Tumours Other Than Lymphomas and Breast Cancer

J.P. Droz and P. Biron

HIGH DOSE chemotherapy (HDCT) was developed on the basis of technology for providing haematological support. Autologous bone marrow transplantation (ABMT) became available in the mid-70s, and more recently the development of haematopoietic growth factors and peripheral blood stem cell support have allowed studies in a broad range of tumours. The first studies were carried out in non-Hodgkin's lymphoma and breast cancer, and subsequently, studies in germ cell tumours, ovarian cancers, melanoma and central nervous system (CNS) tumours were published. We will focus on high-dose chemotherapy in these tumours in adulthood.

## GERM CELL TUMOURS (GCT)

GCT are very chemosensitive, with the following drugs having significant activity: etoposide (ETO), oxazaphosphorine derivatives (ifosfamide [IFO] and cyclophosphamide [CYCLO]) and platin derivatives (cisplatin [PLAT] and carboplatin [CARBO]). Attempts have been made to increase the dose of ETO, either IFO or CYCLO, and either PLAT or CARBO.

The experience of HDCT with ABMT involved hundreds of patients in the salvage setting [1]. It can be concluded from these studies that dose escalation of ETO and platin derivatives allows increased activity of these drugs; that patients who are cisplatin-refractory are very unlikely to enter long-term remission status (less than 10% of patients), and that patients who are still cisplatin-sensitive can be cured by HDCT (30–40% of long-term remission patients) [2]. An international randomised study has been designed to demonstrate the potential role of consolidation HDCT in the salvage setting.

Trials studying the role of HDCT as first line treatment of poor risk patients have failed to demonstrate the benefit of dose intensification [3]. A randomised trial which is investigating two cycles of high-dose ETO with CARBO in this setting is currently on-going in the U.S.A.

## OVARIAN CANCER

Ovarian cancer is very chemosensitive and a number of drugs are active including alkylating agents, anthracyclines and platin derivatives. Several drugs have been studied at very high doses

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with bone marrow support: melphalan (MEL), thiotepa (TTP), CYCLO, IFO, CARBO, PLAT and ETO.

Since 1984, many series involving several hundreds of patients with advanced stage ovarian cancer have been published. It is noteworthy that the clinical CR rate and pathological CR rate with first-line conventional chemotherapy is 40 and 20%, respectively, while after salvage chemotherapy, less than 10% of patients obtain CR. This compares with an objective response rate after HDCT with ABMT of 70–80% [4], although median duration of response remains less than 12 months.

It is thus interesting to study the role of HDCT with ABMT in the first-line setting. Is there a role for HDCT as consolidation treatment in negative second-look laparotomy patients? Is there a role for HDCT with ABMT to convert microscopic disease-positive second-look laparotomy patients to CR? These hypotheses are tested in on-going prospective randomised trials.

## SMALL-CELL LUNG CANCER

The prognosis of both limited disease (LD) and extensive disease (ED) small-cell lung cancer (SCLC) is poor, with only a small proportion of LD patients alive at two years. However, SCLC is a very chemosensitive tumour with the most active agents being anthracyclines, ETO, alkylating agents (CYCLO), vinca alkaloids and platin derivatives (PLAT, CARBO). After conventional chemotherapy, the objective response and CR rates are 90 and 40%, respectively [5], with the majority of patients relapsing due to the acquisition of a resistant phenotype. The role of HDCT with ABMT has been tested in the consolidation setting with neither phase II nor phase III trials demonstrating any survival advantage for this approach, although only one randomised trial addressing this question has been published [6]. Both LD and ED SCLC have been treated by induction conventional chemotherapy (CYCLO + methotrexate + lomustine alternating with vincristine + doxorubicin + procarbazine). Responding patients were randomised to receive either further conventional chemotherapy or one cycle of HDCT with ABMT (CYCLO: 6g/m$^2$, ETO: 500 mg/m$^2$, carmustine: 300 mg/m$^2$). Of 101 patients, 45 were randomised to receive late intensification. Median survival after induction chemotherapy was not statistically different, however, the survival of patients who were submitted to HDCT with ABMT was slightly longer, this being more evident in LD patients. It is noteworthy that only a small proportion of patients may be suitable for HDCT with ABMT, with poor performance status the major limiting factor.

## GLIOMA

The standard treatment of high dose glioma is both surgery and radiotherapy, but survival remains poor [7]. Several prognostic factors relating to survival have been described. The most active drugs at conventional doses are nitrosoureas and ETO. The major experience with HDCT with ABMT is based on the use of high-dose nitrosoureas: BCNU and fotemustine. Other attempts have been made with CCNU, ACNU, ETO and TTP. The dose of BCNU is 600–1200 mg/m$^2$, and that of fotemustine 800 mg/m$^2$. In recurrent disease, the objective response and CR rates are 40% and less than 10%, respectively, and survival is short (median 4 months).

Several studies have reported the results of HDCT with ABMT, either immediately after surgery and before radiotherapy or as adjuvant treatment after radiotherapy. In these studies, it is difficult to evaluate objective response rate, but median survival is approximately 16 months, with a two year survival of 30–40%.

## MELANOMA

Different phase II trials with high-dose alkylating agents (BCNU, melphalan, TTP) and ABMT show that the complete response rate is high, 30–70% [8], but the duration of response short (median 5 months). Several studies have explored combined treatment modalities with high-dose alkylating agents and ABMT followed by IL2, although the toxicity of such an approach is high.

It is concluded from the experience in such tumours that high-dose chemotherapy with ABMT has some activity, but fails to improve patient survival. New trials will assess the potential role of very intensive repeated doses of cytotoxic agents with peripheral stem cell support.

A consensus conference has recently stated that high dose chemotherapy should not be considered as a standard therapeutic option in these tumour types and should only be carried out within the setting of a prospective trial [9].


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