High dose chemotherapy for childhood solid tumours: lessons to learn and future developments

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Malignant solid tumours, commonly observed in children, usually display a very high proliferative index. This is particularly true if embryonal tumours are considered. This condition is one of the major biological factors relating to chemosensitivity of these tumours specifically observed in children. During the last 30 years, the large use of adjuvant and neoadjuvant chemotherapy has resulted in major improvements in the prognosis of cancers in children. From 25% at the end of the 1960s, 75% of children treated for cancer were long- term survivors at the beginning of the twenty first century. Nevertheless, the 25% of failure in paediatric cancers remained a challenge and new therapeutic approaches had to be explored for these poor prognostic cases. The analysis of these cases revealed that this high-risk population comprised of at least two subgroups. One group constituted of tumours for which almost no effective chemotherapeutic drug had been described such as brain tumours. The other high-risk subgroup concerned patients affected by chemosensitive tumours but were complicated either by a relapse or by the presence of metastases at diagnosis. For this second subgroup of patients, it appeared necessary, and possibly promising, to test the dose-response relationship. The relation between the dose of drug and the response had been studied *in vitro* on cell lines, and was specifically observed when alkylating agents were used. During the same period, at the end of the 1970s; the technique of cryopreservation of bone marrow stem cells was developped and its viability was demonstrated. Hence it was possible to use cryopreserved autologous bone marrow cells to rescue the otherwise lethal hematologic toxicity related to the administration of very high-doses of alkylating agents. Thirty years after these first investigations what has been learned and what are the future directions?

Any improvement in the prognosis of poor-risk childhood solid tumours?

Several types of malignant disease had been approached using this strategy. Apart from lymphomas (Hodgkin' s disease and Non Hodgkin' s Lymphomas) several types of tumours have been investigated but the most representatives are neuroblastomas, Ewing' s family and brain tumours.

Neuroblastoma

In neuroblastoma, the patients presenting metastases at diagnosis constitute about 60% of the entire population; 90% of them being over one year of age at diagnosis. Under conventional therapy, the five-year overall survival (OS) is between 5% and 15% according to different studies. The use of high-dose chemotherapy (HDC) as consolidation of first remission permitted to improve significantly the prognosis. At the present time, the five-year OS is close to 40%. This improvement has been confirmed by a prospective randomised study. Age at diagnosis; status at the time of transplant; and the type of conditioning regimen are the most relevant prognostic factors. Similarly, for the non metastatic forms of the disease, the major poor prognostic value of MYCN oncogene amplification has been recognised. The use of a high-dose consolidation, similar to that described for metastatic patients, was followed by a similar improvement in long-term survival. A present, European randomised study is prospectively evaluating the value of two different regimens for all high-risk neuroblastoma patients.

Even if this approach permitted a real step forward, the treatment of these patients remains a challenge. The use of maturating agents is a promising way. For the future, new drugs, monoclonal antibodies are presently tested to build multimodal approach of this disease.

Ewing tumours

In this family, the bone tumours (' Ewing Sarcoma') are the most frequent in childhood. In this disease several prognostic factors have been descibed after

analysis of large populations treated with conventional treatment in a European cooperative study group. The major poor prognostic factor is the presence of metastases at diagnosis. The multifocal spread of the disease is one additional poor prognostic factor in metastatic patients. In the non-metastatic situation, poor histological response to neoadjuvant chemotherapy is related with a very poor prognosis. For these high risk groups, the use of HDC consolidation with stem cell support increased the 5-year OS from 10% to about 50%. The Busulfan Melphalan combination appears to be the best conditioning regimen. To evaluate prospectively the role of this approach in Ewing tumours, the European group is randomly comparing HDC with stem cell support to conventional prolonged maintenance therapy. Inclusion started in 1999 and is still open for few more months.

For the future, the precise analysis of the specific translocation observed in this disease should soon open new ways of treatment using targeted therapy. For the most severe cases (multifocal metastases) tandem high-dose chemotherapy is presently under investigation.

Brain tumours

Brain stem malignant gliomas

In these tumours, until now, only radiation therapy is recognised to be temporarily efficient where the median survival is short (10 months) and the long-term survival is close to zero. The role HDC with stem cell support as been prospectively studied after primary radiotherapy as adjuvant therapy, it showed however that the survival was absolutely similar and demonstrated once again tumour chemoresistance. Hopefully, a better understanding of the biology of this tumour will allow new specific approach using targeted therapy.

Medulloblastoma

This is the most frequent brain tumour in childhood and most children are under 5 years of age at diagnosis. Cranio-spinal irradiation is the gold standard for the treatment of this disease, but the very severe cognitive late effects observed in children irradiated before 5 years of age are increasingly being considered unacceptable. For this reason, several teams have evaluated the role of post-operative, long lasting conventional chemotherapy to postpone or to avoid cranio-spinal irradiation. With this strategy about 40% of patients remained in long lasting remission without irradiation and 60% relapsed. The incidence of relapse is much higher in patients with metastatic disease at diagnosis. HDC with stem cell transplantation (SCT) support has been extensively studied in the treatment of relapses. A single course, combined with local irradiation, appeared very efficient to control local relapses with the majority of patients surviving. In these long lasting survivors, the severity of the cognitive late effects could be lowered but a longer follow-up is necessary to evaluate the very long term effects. Conversely a single course of HDC used to treat patients with detectable metastases was unsuccessful. At the present time, for the very high-risk group of young children the use of sequential high-dose chemotherapy followed by multiple SCT is prospectively evaluated.

Thus, it now appears that medulloblastoma is a chemosensitive disease and that some selected high-risk patients could be cured without cranio-spinal irradiation. However, the long term benefit remains to be demonstrated, the long term sequela being related not only to cranio-spinal irradiation but also to several other factors related to the disease and the treatment. Nevertheless for the future, these tentative steps opened the way to chemotherapy in the treatment of central PNET. HDC appeared at least as efficient as cranio-spinal irradiation as ' prophylactic treatment' of the metastatic disease. The use of high doses permitted transport across the blood brain barrier. In the near future, a better definition of high-risk patients within the central PNET will be obtained according to genetic analysis results patient tumour tissues. It will then become possible to propose an aggressive strategy earlier in the course of treatment of high-risk patients.

At the present time, the use of HDC with SCT in high-risk tumours in children is much more common than during the 1980s. Furthermore it progressively became part of the primary treatment before any relapse. This evolution was related to the significant improvements in supportive care during this period of time. They were, in particular related to two important innovations: the use of granulocyte growth factors (G-CSF) and the use of peripheral blood stem cells (PBSC) instead of bone marrow cells for the graft. Several studies have demonstrated that G-CSF administered after transplantation significantly shortened the duration of granylocytopenia. The use of PBSC drastically changed the evolution of early post-transplant complications. These innovations along with the use of more efficient anti-infective therapies permitted to significantly lower the transplant related death rate.

For the future, several problems remain to be solved. For the prevention of mucositis, preliminary results on the use of keratinase growth factor (KGF) in

adults appear very promising. Similarly, the use of prophylactic defibrotide could decrease the incidence and the severity of hepatic veno-occlusive disease. *In vitro* expansion of the graft would perhaps allow a further reduction of the duration of post-transplant aplasia. *In vitro* manipulation of immunologic effector cells of the graft could allow the combination of cytoreductive therapy and amplification of immune responses against minimal residual disease. Finally, during the next 10 years, given the plasticity of hematopoietic stem cells, the role of cell therapy would become much larger and not merely restricted to the reconstitution of hematopoiesis.